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Structure, regulation, and (patho-)physiological functions of the stress-induced protein kinase CK1 delta (CSNK1D)

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Abstract

Members of the highly conserved pleiotropic CK1 family of serine/threonine-specific kinases are tightly regulated in the cell and play crucial regulatory roles in multiple cellular processes from protozoa to human. Since their dysregulation as well as mutations within their coding regions contribute to the development of various different pathologies, including cancer and neurodegenerative diseases, they have become interesting new drug targets within the last decade. However, to develop optimized CK1 isoform-specific therapeutics in personalized therapy concepts, a detailed knowledge of the regulation and functions of the different CK1 isoforms, their various splice variants and orthologs is mandatory. In this review we will focus on the stress-induced CK1 isoform delta (CK1 δ), thereby addressing its regulation, physiological functions, the consequences of its deregulation for the development and progression of diseases, and its potential as therapeutic drug target.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gene.2019.144005>.

Keywords

Casein kinase 1; CSNK1D; Phosphorylation; S; Small molecule inhibitor; R; P; Site-specific phosphorylation; Stress-induced kinase; p53; Wnt signaling pathway; Hedgehog pathway; Cancer; N

1. Introduction

CK1δ, a member of the CK1 (formerly named casein kinase 1) family, has been first isolated by Graves and colleagues in the early 1990s. The human gene encoding CK1δ (*CSNK1D*) is located on the long arm of the chromosome 17 (17q25.3) (Graves et al., 1993). In the last decades the roles of CK1δ have been characterized more and more, both in physiological and in pathologic conditions. In fact, dysregulation of the expression and activity of CK1δ has been observed in different types of cancers, as well as in different neurological disorders, among them Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS). CK1 isoforms δ and ε exhibit high identity within their kinase domains but no differences of their functional roles were detected in several early studies. Even though it still remains challenging to assign distinct functions to one of the human CK1 isoforms (α, γ₁₋₃, δ, ε), new studies are now focusing on this issue. Considering the fact that even CK1δ transcription variants (TVs) exhibit different functions, there is a need to clearly state, which isoform or even TV has been used to receive detailed information and to increase reproducibility of the data by other researchers (Fustin et al., 2018; Narasimamurthy et al., 2018). From this point of view there is a high demand to develop highly specific, isoform- or even TV-specific therapeutics which could be of use in personalized therapy concepts for the treatment of neurodegenerative diseases and cancer. The present review will focus on CK1δ, its regulation, functions, its relevance in human diseases, and as a target for drug development.

2. Genetic coding of CK1δ

Historically, the initial gene sequence of CK1δ was isolated by Graves et al. in form of cDNA from the testicles of rats in the year 1993. The gene construct was sequenced and characterized as a 1284 nucleotide sequence transcribing into a 49 kDa protein consisting of 428 amino acids (aa) (Graves et al., 1993). This sequence was followed by the human gene construct with 1245 nucleotides describing a protein containing 415 aa (Kusuda et al., 1996). In the following years CK1δ was discovered and described in yeasts, various animals, plants, and even parasites (Barik et al., 1997; Donald et al., 2005; Allocco et al., 2006; Urbaniak, 2009; Rachidi et al., 2014; Dorin-Semblat et al., 2015) (Table 1).

Although there are various variants of CK1δ in different organisms, three different TVs of CK1δ are present in humans, in rat (*Rattus norvegicus*) and in mice (*Mus musculus*).

All three different CK1δ TVs expressed in human, rat, and mouse do not differ in their amino acid sequences until position 381. After position 399 three distinct sequences for the respective TVs can clearly be distinguished as illustrated in Fig. 1.

The Clustal Omega algorithm (Madeira et al., 2019) identifies three distinct sequences that are shared between the three different organisms: the shortest sequence containing 409 aa (TV2 in humans and rat as well as CRAc in mouse), followed by a sequence consisting of 415 aa (TV1 in humans and rats/CRAa in the mouse), and a sequence containing 428 aa for the mouse (CRAb) and the rat (TV3) homolog as well as a human TV3 sequence, which is missing one aa at the second to last position, resulting in a length of 427 aa.

In addition to the shown sequences of human, rat, and mouse, CK1δ sequences in most eukaryotic organisms are homologous. The phylogenetic tree displayed in Supplementary Fig. 1 resembles the degree of evolutionary relationship between various sequences of CK1δ.

2.1. Analysis of transcription variants of CK1δ

Various TVs of the gene *CSNK1D* have been described in the “Mammalian Gene Collection”. Two different TVs of CK1δ were postulated during the early analysis of human and murine genes in 2002 (Strausberg et al., 2002). Since then TV1 (accession number: AAH03558.1, GI: 13097702) and TV2 (accession number: AAH15775.1, GI: 16041786) have been well described in literature. Recently, it could be clearly shown that both variants exhibit opposite functions in the circadian rhythm (Fustin et al., 2018). Both sequences are highly homologous and are alike for the first 399 aa, but differ at the following 16 aa for TV1 and ten aa for TV2, respectively. They do share the first eight exons. The variance occurs due to the fact that TV1 is finished by exon 10, while TV2 uses exon 9. TV2 also includes exon 10, but after the first ten amino acids of exon 9 a stop codon halts the translation and prevents the translation of exon 10 (Fig. 2).

Additionally, a third human TV (TV3, accession number: NP_001350678.1, GI: 1393428169), which is very similar to the original CK1δ rat sequence published by Graves and colleagues (Graves et al., 1993), can be found on chromosome 17 (accession number: NG_012828.2, GI: 1428083528). TV3 uses exon 11 instead of 9 and 10. Exon 11 is located downstream of exon 10 and is overlapping with the gene *Slc16a3*. However, exon 11 is located in a non-coding area. The use of the different exons resulting in the three transcription variants is depicted in Fig. 2.

The inclusion of exon 11 used for TV3 increases the initially postulated length of the CK1δ gene (*CSNK1D*) from 29.3 kb to approximately 35 kb, which means the length is similar to the rat *CSNK1D* gene with 34.6 kb.

All three transcription variants were identified in 2014 by the data bank analysis approach by Ezkurdia et al. (2014). Even though the study combined the detection of cellular protein expression by peptide mass spectrometry with the protein-coding potential of the genome, at that time no specific evidence was provided indicating that all three TVs are actually translated. Furthermore, TV3 is listed as “unreviewed” entry in the UniProtKB data base (H7BYT1_HUMAN).

2.2. Polyadenylation patterns of transcription variants

Analysis of polyadenylation sites using the tool RegRNA 2.0 for identification of functional RNA motifs (Chang et al., 2013) revealed that TV1 and TV2 share the same polyadenylation pattern downstream of the stop codon on exon 10, starting at position 1246. The identified motif is 32 nucleotides long (AGUAGAGUCUGCGCUGUGACCUUCUGUUGGGC).

Since exon 10 is not present in TV3, a 32 nucleotides long sequence (AGUGGCUUGUCCACCUCAGCUCCCAUCUAAC) located downstream of the stop codon on exon 11, at the starting nucleotide 320, is used. The various motifs result in different minimum free energy values (−28.70 kcal/mol for TV1 and TV2, and −16.03 kcal/mol for TV3). The predicted RNA folding structures of the respective motifs with flanking regions are depicted in Fig. 3.

3. CK1δ structure and domains

As an own family within the superfamily of serine/threonine-specific kinases all CK1 members are composed by two lobes, basically building all eukaryotic protein kinases (ePKs): the N-terminal lobe (N-lobe) mainly consists of β -sheet strands while the larger C-terminal lobe (C-lobe) is mainly composed by α -helices and loop structures (Fig. 4). Apart from five twisted antiparallel β -strands (β 1– β 5), the N-lobe also contains a prominent α -helix (α A) crucial for conformational regulation of kinase activity. Within the C-lobe, loop L-78 has previously been attributed to the modulation of CK1 inhibitor selectivity (Peifer et al., 2009) and binding of a tungstate derivative (as a phosphate analog) identified a recognition motif (W1) for the binding of phosphorylated substrates. Major sites involved in mediating substrate recognition are Arg-178, Gly-215, and Lys-224. Positively charged side chains of Arg-178 and Lys-224, but also Lys-217, Lys-221, and Arg-222 enable the formation of ionic interactions with acidic or phospho-primed substrates. This also applies for binding of the C-terminal domain to the substrate binding region for the purpose of autoregulatory function (Longenecker et al., 1996). Upon substrate binding the phospho-acceptor group of the targeted Ser/Thr residue is directed to the γ -phosphate of simultaneously bound ATP, located in close proximity within H-bonding range. Also loop L-EF is putatively involved in substrate recognition and binding, although some residues of this loop could not be modelled in several studies due to poor electron density. Therefore, this loop has been found to be partially disordered in previously performed analyses of CK1δ structure (Longenecker et al., 1996; Zeringo et al., 2013). Additionally, residues Asn-172 and Thr-176 seem to be crucial for substrate binding and/or kinetic activity of CK1δ. The amino acid exchange N172D was identified by analyzing the CK1δ sequence of the simian virus 40 (SV40)-minimally transformed rat fibroblast cell line Rev2. The substitution of asparagine by aspartic acid is supposed to significantly alter the electrostatic potential of the protein surface from neutral to acidic, resulting in impaired kinase activity (Hirner et al., 2012). Within the same region of this substrate binding area also residue Thr-176 can be found. A point mutation leading to the amino acid replacement T176I was originally identified in Hrr25, the CK1δ ortholog in *Saccharomyces cerevisiae* (Murakami et al., 1999). This amino acid exchange resulted in a loss-of-function phenotype with only little residual kinase activity and has been used in various studies in order to create mutants of

CK1δ with insufficient kinase activity (Murakami et al., 1999; Milne et al., 2001; Mehlgarten and Schaffrath, 2003).

A catalytic cleft for binding of substrates and ATP is formed between the N- and C-terminal lobe of CK1, which are connected *via* a hinge region (Xu et al., 1995; Longenecker et al., 1996). The ATP active site is formed by two binding regions: a deep hydrophobic pocket (HPI, also known as selectivity pocket) and a second spacious hydrophobic region (HRII). Furthermore, sugar and phosphate binding domains can be found in the ATP active site (Peifer et al., 2009). The glycine-rich P-loop contains the motif Gly-X-Gly-X-X-Gly and bridges strands β1 and β2 (L-12) by forming a β-strand-turn-β-strand motif. This P-loop builds the top cover of the ATP binding site, usually holds the non-transferable phosphate of ATP in place, and is assumed to be more flexible as long as no ATP is present in the ATP binding pocket (Hantschel and Superti-Furga, 2004; Zeringo et al., 2013).

Residues directly involved in forming interactions in the ATP binding site have been analyzed by Singh and Gupta (Singh and Gupta, 2015). In this study the incomplete structure of CK1δ has initially been completed by homology modeling (starting from the structure of CK1α). By using FTSiteserver active site residues Gly-18, Ser-19, Phe-20, Asp-22, Lys-38, Leu-39, Glu-40, Gln-48, Leu-49, and Glu-52 were predicted for the newly created CK1δ structure, termed dCK1-M (Singh and Gupta, 2015). Lysine residue 38 is also conserved in isoforms CK1α (Lys-46) and CK1ε (Lys-38) and is crucial for ATP binding and kinase activity, since substitution of this residue, usually by arginine or methionine, completely abolishes kinase activity creating a kinase-dead CK1δ mutant (Rivers et al., 1998; Budd et al., 2000; Milne et al., 2001; Zeringo et al., 2013; Singh and Gupta, 2015). Furthermore, the so called catalytic loop (L-67) with the sequence Asp-Val-Lys-Pro-Asp-Asn (amino acids 128–133) is also essential for ATP binding. Residue Asp-128 can even be considered as catalytic base (Xu et al., 1995; Zeringo et al., 2013) (Fig. 5).

Kinase activity of eukaryotic protein kinases in general can be regulated by conformational changes affecting the so called activation loop, which in the case of CK1δ is represented by loop L-9D (Xu et al., 1995; Longenecker et al., 1996). Switching to an active conformation, the activation loop moves out of the catalytic site and the aspartate residue of the DFG motif (residues Asp-149, Phe-150, and Gly-151 in the case of CK1δ, located in loop L-89) shifts to an internal position. There, the aspartate of this highly conserved motif chelates a Mg²⁺ ion essential for ATP binding and orientation (Endicott et al., 2012). Another conserved eukaryotic protein kinase motif, the APE motif at the end of the activation loop, is modified in CK1δ and is represented by the SIN motif in helix αD (Hanks and Hunter, 1995). In conclusion, residues Lys-38, Lys-130 (catalytic loop residue), Asp-149 (DFG residue), and the P-loop act together to form interactions with the triphosphate moiety of ATP.

In addition, especially for the regulation of kinase activity, as well as for forming interactions with small molecule inhibitors, several residues of CK1δ encoded by exon 3 are essentially involved (Long et al., 2012; Richter, Ullah et al. 2015). One of them is the so called gatekeeper residue located directly within the ATP binding pocket. While the catalytic activity of the kinase usually is not affected by the size of the gatekeeper side chain, the affinity of small molecules, and their access to certain binding pockets (selectivity pockets)

beyond the gatekeeper position can be limited by gatekeeper mutations. In the case of CK1 δ residue Met-82 (located in loop L-5B) takes the role of the gatekeeper and substitution to the more space-filling residue phenylalanine (M82F) actually abolished binding of a certain class of imidazole-based inhibitors to the selectivity pocket (HPI) in the ATP active site of CK1 δ (Peifer et al., 2009).

In other studies however, increased affinity of benzimidazole- and benzothiazole-based inhibitors to the CK1 δ M82F gatekeeper mutant could be observed, caused by additional π -hydrogen bonds or π -stacking interactions between Phe-82 and the inhibitor molecules (Bischof et al., 2012; Garcia-Reyes et al., 2018). For another CK1 δ point mutation localized in exon 3 resulting in S97C substitution the loss of ATP binding affinity has been detected by molecular dynamics simulations and docking studies, respectively (Kumar et al., 2014). In contrast, a CK1 δ T67S mutant displayed increased kinase activity *in vitro* and enhanced oncogenic potential in cell culture experiments and in a subcutaneous tumor xenotransplantation model. Moreover, CK1 δ T67S showed increased sensitivity toward CK1-specific inhibitors (Richter, Ullah et al. 2015).

Besides substrate and ATP binding regions further functional domains being involved in mediating protein-protein interactions are located in the CK1 δ protein. Additionally, the kinase domain, which extends between amino acids 9 to 277, contains a kinesin homology domain (KHD) as well as a putative dimerization domain (DD). The DD includes residues from β -strands β 1, β 2, β 3, and β 7, as well as from loops L-12, L-78, helix α B, and the hinge region (Longenecker et al., 1998). The KHD, located within the activation-loop (L-9D), is supposed to mediate interactions between CK1 isoforms and components of the cytoskeleton (Roof et al., 1992, Xu et al., 1995, Behrend et al., 2000b). At the junction between L-EF and the α F-helix also a nuclear localization signal sequence (NLS) is located which, however, is not sufficient for nuclear localization of CK1 δ (Hoekstra et al., 1991; Graves et al., 1993). Finally, a centrosome localization signal (CLS) domain can be found between residues 278 and 364 (Greer and Rubin, 2011).

Because sequences of human CK1 δ TV1, 2, and 3 are fully conserved up to amino acid 399 structural elements described so far can be found in all variants (sequence alignment of human CK1 δ TV1, 2, and 3 can be found in Fig. 1A). Unfortunately, analysis of the three-dimensional structure of CK1 δ has only been performed with truncated proteins *e.g.* terminating at amino acids 295 or 318, respectively. This procedure is necessary in order to circumvent problems occurring due to C-terminal proteolysis and variable (auto-)phosphorylation states of the full-length protein (Longenecker et al., 1996). Although these proteins still contain the full kinase domain, however, no validated structural data regarding the C-terminal domain could be made available so far.

4. Regulation of CK1 δ activity

Because CK1 δ is ubiquitously expressed and its activity is essential for proper function of several important cellular signal transduction pathways, its expression and activity needs to be strictly controlled. First of all, expression of CK1 δ varies between different tissues and cell types and is related to certain physiological and pathophysiological conditions and

stimuli (Lohler et al., 2009). DNA-damaging substances like the topoisomerase inhibitors etoposide and camptothecin, as well as γ -irradiation, resulted in tumor protein 53 (p53)-dependent increased levels of CK1 δ mRNA (Knippschild et al., 1997; Behrend et al., 2000b). Furthermore, gastrin has been shown to induce CK1 δ /e-mediated phosphorylation of protein kinase D2 (PKD2) (von Blume et al., 2007), while elevated CK1-specific activity in general has been detected in cells upon stimulation with insulin (Cobb and Rosen, 1983) or viral transformation (Elias et al., 1981).

Apart from transcriptional or translational control of CK1 δ protein expression, its kinase activity can also be regulated at protein level by sequestration to particular subcellular compartments, interaction with other proteins, and posttranslational modifications.

By sequestration of CK1 δ to distinct subcellular compartments well defined pools of substrates can be made available to the kinase in order to guide its activity toward specific functions (Wang et al., 1992; Vancura et al., 1994; Sillibourne et al., 2002). Subcellular sequestration is mainly mediated by scaffolding structures containing distinct interaction motifs. In general, the purpose of these scaffolds is to bring interacting molecules into close proximity within interaction complexes in order to enable their orchestrated function in certain signal transduction pathways. Additionally, these scaffolds are supposed to allosterically control the activity of their interaction partners (Locasale et al., 2007; Good et al., 2011).

One of these scaffolds involved in sequestration of CK1 is A-kinase anchor protein (AKAP) 450 (also known as AKAP350, AKAP9, or centrosomal and Golgi N-kinase anchoring protein [CG-NAP]). AKAP450 has been shown to specifically interact with CK1 δ and e, resulting in recruitment of both isoforms to the centrosome to exert centrosomespecific functions contributing to cell cycle regulation (Sillibourne et al., 2002; Greer and Rubin, 2011). Moreover, interaction of AKAP450 and CK1 δ has been demonstrated as one mechanism essential for primary ciliogenesis (Greer et al., 2014). As another example, previously identified as a scaffolding adaptor activating the inhibitor κ B kinase (IKK), X-linked DEAD-box RNA helicase 3 (DDX3X) has been shown to promote CK1 ϵ -mediated phosphorylation of Dishevelled (Dvl) in the canonical Wingless/Int-1 (Wnt) signal transduction pathway (Cruciat et al., 2013; Gu et al., 2013). Apart from CK1 ϵ , DDX3X also has the potential to increase the activity of CK1 δ by up to five orders of magnitude, thereby representing an important co-factor for CK1-mediated Wnt-specific functions (Cruciat et al., 2013). Additional interacting proteins were identified in a study screening for interaction partners that direct CK1 δ to ubiquitinated lesions of Alzheimer's disease. These all contained a common single open reading frame which was termed casein kinase-1 binding protein (CK1BP). Sequence alignment demonstrated that CK1BP is structurally homologous to the acidic domain of dysbindin, a component of dystrophin-associated protein complex (DPC) and biogenesis of lysosome-related organelles complex-1 (BLOC-1). CK1BP inhibits CK1 δ kinase activity in a dose-dependent manner as demonstrated for the *in vitro* phosphorylation of tau and α -synuclein (Yin et al., 2006). Interestingly, interaction with heparin has been reported to activate CK1 δ *in vitro*. Heparin presumably interacts with the C-terminal regulatory domain and finally prevents autoinhibition. Although being unlikely to represent a physiological regulator of CK1 δ kinase activity, experiments performed with

heparin impressively demonstrate the autoinhibitory potential of the C-terminal domain (Graves et al., 1993; Cegielska et al., 1998).

Dimerization of CK1 δ can also be seen as a mechanism for regulation of enzymatic activity and is made possible *via* an extensive dimer interface inside the DD. In more detail, an α -helix from the CK1 δ C-lobe binds to the hydrophobic cavity in the N-lobe of a second CK1 δ protein (Ye et al., 2016). Finally, the binding of ATP and perhaps also the binding of large substrates is prevented by Arg-13 inserting into the adenine binding pocket upon dimerization (Longenecker et al., 1998). In solution, CK1 δ is always purified as a monomer leading to the question if dimerization can actually be considered biologically relevant. However, dimerization of CK1 δ has been confirmed by studies in which kinase activity of endogenous CK1 δ was down-regulated by binding of a transfected/transgenic dominant-negative and less active CK1 δ mutant (Hirner et al., 2012). Interestingly, also a kinase-dead mutant of CK1 ϵ demonstrated dominant-negative potential, leading to the conclusion that dimerization as a regulatory mechanism is not restricted to CK1 δ (Cerdeira et al., 2015). Results of a study analyzing the interaction between the yeast (*Saccharomyces cerevisiae*) CK1 δ ortholog Hrr25 and the meiosis-specific monopolin subunit Mam1 even led to the hypothesis that the hydrophobic dimerization site may be a conserved site for the binding of recruiters or regulators in general (Ye et al., 2016).

As a measure to reversibly modulate and fine-tune kinase activity also in the short term, CK1 δ can be postrationally modified either by intramolecular autophosphorylation or site-specific phosphorylation by upstream cellular kinases (Fig. 6). Generally, CK1 kinase activity is decreased upon (C-terminal) phosphorylation and can be regulated *in vivo* by the action of kinases and phosphatases (Rivers et al., 1998). Autophosphorylation processes result in the generation of sequences with the motif pSer/pThr-X-X-Y (X stands for any amino acid while Y stands for any amino acid except serine or threonine). These motifs can subsequently act as pseudo-substrates blocking the catalytic center of the kinase. Within the C-terminal domain of CK1 δ residues Ser-318, Thr-323, Ser-328, Thr-329, Ser-331, and Thr-337 were identified as candidate sites targeted by autophosphorylation (Graves and Roach, 1995; Rivers et al., 1998). The presence of an autoinhibitory domain is furthermore confirmed by the observation that proteolytic cleavage of the C-terminal domain results in increased CK1 kinase activity *in vitro* (Carmel et al., 1994; Graves and Roach, 1995). As a mechanism leading to dephosphorylation of inhibitory C-terminal autophosphorylation sites activation of group I metabotropic glutamate receptors (mGluRs) was identified. Following activation of mGluRs Ca^{2+} -dependent stimulation of the phosphatase calcineurin finally initiates dephosphorylation. Although the underlying study was performed using CK1 ϵ the respective target sites are also conserved in CK1 δ (Liu et al., 2002).

Within the last decade also site-specific phosphorylation of CK1 δ by upstream kinases has been extensively described and target sites have been identified. However, most of these studies were only performed *in vitro* and final proof for site-specific phosphorylation *in vivo* is pending in many cases. Within the C-terminal domain of CK1 δ Ser-370 could be detected as major residue targeted by protein kinase A (PKA), protein kinase B (PKB/Akt), CDC-like kinase 2 (CLK2), protein kinase C α (PKC α), and checkpoint kinase 1 (Chk1) (Giamas et al., 2007; Bischof et al., 2013; Meng et al., 2016). CK1 δ kinase activity was enhanced after

mutation of Ser-370 to alanine (S370A) and the key role of Ser-370 was furthermore demonstrated *in vivo* by expressing a S370A mutant of CK1δ in *Xenopus laevis* embryos. By affecting Wnt/β-catenin-mediated signal transduction overexpression of the hyperactive S370A mutant led to enhanced formation of an ectopic dorsal axis in *Xenopus* embryos (Giamas et al., 2007).

Apart from Ser-370 site-specific phosphorylation of CK1δ by Checkpoint kinase 1 (Chk1) has additionally been identified for Ser-328, Ser-331, and Thr-397. Also for these sites mutation to alanine resulted in significantly increased kinase activity (Bischof et al., 2013). Ser-328 and Thr-329 were also identified to be targeted by PKCα. Mutation of Ser-328, Thr-329, and Ser-370 to alanine significantly affected the kinetic parameters of CK1 and resulted in an increase of the catalytic efficiency (k_{cat}/K_m) as well, which was most impressive for S328A and T329A (Meng et al., 2016).

Cyclin dependent kinase 2/cyclin E (CDK2/E) and cyclin dependent kinase 5/p35 (CDK5/p35) were also identified as cellular kinases able to modulate CK1δ activity through site-specific phosphorylation within the C-terminal domain. Phosphorylation of Ser-331 and Thr-344 by CDK2/E has been shown by two independent methods, while phosphorylation of Thr-329, Thr-347, Ser-356, Ser-361, and Thr-397 finally could not be confirmed. Furthermore, no clear evidence could be generated confirming phosphorylation of Thr-329, Thr-344, Thr-347, Ser-356, Thr-397 by CDK5/p35 (Ianes et al., 2016). Recently however, Eng et al. identified Thr-347 to be phosphorylated by CDKs (Eng et al., 2017).

While most studies focused on the identification of phosphorylation sites in the C-terminal domain of CK1δ, potential targeted sites for cellular kinases can also be found in the kinase domain. Recent reports demonstrate that residues Ser-53, Thr-176, and Ser-181 can be phosphorylated by PKCα (Meng et al., 2019, Bohm et al., 2019). Furthermore, phosphorylation of residues Thr-161, Thr-174, Thr-176, and Ser-181 has recently also been demonstrated for Chk1 (Bohm et al., 2019). Subsequently performed enzyme kinetic analysis and experiments pre-incubating CK1δ with either PKCα or Chk1 led to identification of domain-specific effects of PKCα- or Chk1-mediated phosphorylation: while kinase activity can be effectively regulated by site-specific phosphorylation within the C-terminal domain (Bischof et al., 2013, Meng et al., 2016), phosphorylation events occurring in the kinase domain might be involved in fine-tuning kinase activity by regulating interactions of the kinase with different substrates or ATP (Bohm et al., 2019, Meng et al., 2019, Bohm et al., 2019).

When being incubated together with Chk1, PKCα, CDK2/E, or CDK5/p35 the *in vitro* kinase activity of CK1δ is significantly reduced (Bischof et al., 2013; Ianes et al., 2016; Meng et al., 2016). While these observations were only generated *in vitro*, there is also evidence from cell culture-based analyses demonstrating inhibitory effects of site-specific phosphorylation on CK1δ kinase activity. CK1-specific kinase activity was reduced in the fibrosarcoma cell line HT1080 after activating Chk1 by hydroxyurea treatment (Bischof et al., 2013). After treating COLO357 pancreatic cancer cells with the PKC-specific inhibitor Gö-6983 cellular CK1-specific kinase activity was increased (Meng et al., 2016). A similar effect could be observed after treating COLO357 cells with the pan-CDK inhibitor

dinaciclib (Ianes et al., 2016). Furthermore, the CDK-targeted phosphorylation sites Thr-344 and Thr-347 are essential for regulation of CK1 δ activity toward period circadian protein homolog 2 (PER2) and degradation of PER2 was promoted when Thr-344 and Thr-347 were mutated to alanine (Eng et al., 2017).

Although much is known about localization of site-specific phosphorylation of CK1 δ , only very few studies were performed using low-throughput methods and mechanistic investigations. Several phosphorylation sites within CK1 δ were only identified by using high-throughput approaches and proteome-wide screenings without further analysis of the effect of phosphorylation or even the identification of the associated upstream kinase.

By performing proteome-wide analysis also additional posttranslational modifications could be identified for CK1 δ like ubiquitination (Lys-54, Lys-57, Lys-140, and Lys-263), acetylation (Lys-242), and methylation (Arg-335 and Arg-375) (information obtained from PhosphoSitePlus®, Hornbeck et al., 2015) (see Fig. 6). However, until now no specific functions or effects have been linked to the observed modifications.

Recently, the expression of all three transcription variants in human and mouse was clearly shown by using primers specific for TV1, TV2, and TV3, respectively (own unpublished results). Furthermore, Michaelis-Menten kinetics clearly revealed that K_m and V_{max} of the three mouse TVs differ in regard to phosphorylation of both, substrates either containing a canonical (α -casein) (Fig. 7A and Table 2) or a non-canonical consensus sequence (GST- β -catenin¹⁻¹⁸¹) (Fig. 7B and Table 2). TV3 is able to phosphorylate α -casein significantly stronger than TV1. Moreover, β -catenin is significantly stronger phosphorylated by TV3 in comparison to TV1 as well as TV2. These variances could be explained by differences in the degree of autophosphorylation mainly occurring within the C-terminal domains of the different transcription variants ((Bischof et al., 2012) and Fig. 7C). In addition, it also has to be considered that due to sequence differences within their C-terminal regulatory domains the presence of consensus sequences for CK1 δ targeting kinases is varying, resulting in differences of site-specific phosphorylation and consequently, also in altered kinase activity (Bischof et al., 2013). Additionally, the phosphorylation state of CK1 δ is not only modulating kinase activity and functions of the different CK1 δ splice variants, it has also been shown to influence the binding of specific ATP-competitive inhibitors *e.g.* resulting in different IC₅₀ values associated to different phosphorylation states (Bischof et al., 2012; Bischof et al., 2013; Richter et al., 2014).

5. Substrates and substrate recognition

At physiological pH CK1 δ carries positive charges at residues Arg-178 and Lys-224, which are mainly involved in substrate binding, preferentially enabling interactions with acidic substrates. Whereas mammalian CK1 isoforms have so far only been shown to exclusively phosphorylate serine and threonine residues of their substrates, the *Saccharomyces cerevisiae* CK1 δ homolog Hrr25 and *Xenopus laevis* CK1 α have been shown to additionally phosphorylate tyrosine residues (deMaggio et al., PNAS, 1992; Pulgar et al., 1996). Substrates being primed by previous phosphorylation represent the canonical CK1 consensus sequence motif pSer/pThr-X-X(X)-Ser/Thr with X standing for any amino acid

and pSer/pThr for the phospho-primed residue. The Ser/Thr residue to be phosphorylated by CK1 δ is located three to four residues upstream to the primed residue. The primed residue can also be replaced by a cluster of negatively charged acidic residues like aspartic (Asp) or glutamic acid (Glu) (three or four residues). However, phospho-primed motifs are favored over Asp or Glu containing motifs and Asp is favored over Glu (Agostinis et al., 1989; Flotow et al., 1990; Flotow and Roach, 1991; Meggio et al., 1991; Graves et al., 1993).

In addition to the canonical consensus motif alternative sequence motifs have been identified, which can also represent targets for CK1-mediated phosphorylation. One of these motifs is the so-called SLS (Ser-Leu-Ser) motif in which the first serine residue is phosphorylated by CK1. This motif can be found in β -catenin and nuclear factor of activated T cells (NFAT). In both cases the SLS motif is followed by a cluster of acidic amino acids essential for efficient binding to CK1 (Marin et al., 2003). Phosphorylation of β -catenin at Ser-45 has been demonstrated for CK1 isoforms α and δ (Amit et al., 2002) while CK1 isoforms α , δ , and ϵ co-fractionated with the sensitivity to red light reduced 1 (SRR-1) domain of NFAT1 (Okamura et al., 2004). Moreover, the consensus motif Lys/Arg-X-Lys/Arg-X-X-Ser/Thr has been identified in several sulfatide and cholesterol-3-sulfate (SCS)-binding proteins, among them myelin basic protein (MBP), the Ras homolog family member A (RhoA), and tau. SCS-mediated stimulation of CK1 δ -mediated phosphorylation could be observed for the two basic brain proteins MBP and tau, and also for the acidic protein RhoA (Kawakami et al., 2008).

To date, > 150 substrates have been identified to be phosphorylated by members of the CK1 family, at least *in vitro*. Although many substrates can be phosphorylated by more than one CK1 isoform and in many cases it is not possible to assign particular isoforms to particular substrates, Table 3 aims to list substrates, which were identified to be phosphorylated by CK1 δ .

6. Subcellular localization of CK1 δ and interaction with cellular proteins

In cells CK1 δ is distributed within both, the cytoplasm and the nucleus. Increased levels of CK1 δ can permanently be detected in peri-nuclear regions in close proximity to the Golgi apparatus and the trans Golgi network (TGN) (Behrend et al., 2000b; Milne et al., 2001; Greer et al., 2014; Stoter et al., 2014). Depending on cellular conditions CK1 δ can also be temporarily associated to membranes and receptors, transport vesicles, components of the cytoskeleton, centrosomes, or spindle poles (Behrend et al., 2000b; Milne et al., 2001; Lohler et al., 2009; Greer et al., 2014; Wang et al., 2015). Studies using kinase-dead mutants or truncated CK1 δ variants demonstrated that the CK1 δ kinase domain is required for nuclear localization of CK1 δ . However, the present nuclear localization signal (NLS) alone is not sufficient for nuclear localization. Moreover, not only the presence of a kinase domain but also its enzymatic activity is essential for correct distribution of CK1 δ within the cell (Hoekstra et al., 1991; Graves et al., 1993; Milne et al., 2001). This hypothesis has been confirmed for the localization of CK1 δ and its yeast ortholog Hrr25 to centrosomes (Milne et al., 2001; Peng et al., 2015a, Peng et al., 2015b). However, there are also contradicting reports showing that kinase activity is dispensable to target CK1 δ to the centrosome (Qi et al., 2015; Elmore et al., 2018).

Further guidance to distinct subcellular compartments is achieved by interaction of CK1 δ with interacting and scaffolding proteins. These interactions are mediated by docking motifs like the Phe-X-X-X-Phe motif, which has been identified in NFAT, β -catenin, and PER proteins, or the Ser-Gln-Ile-Pro motif present in microtubule plus-end-binding protein 1 (EB1) (Vielhaber et al., 2000; Okamura et al., 2004; Bustos et al., 2006; Etchegaray et al., 2009; Zyss et al., 2011). Although some of these proteins are also substrates for CK1 δ -mediated phosphorylation the docking motifs are not necessarily localized adjacent to the phosphorylated residues, but contribute to proper orientation of the interaction partners and to stabilization of the interaction (Bustos et al., 2006). Another protein containing the Phe-X-X-X-Phe interaction motif is family with sequence similarity 83 member H (FAM83H), which has originally been identified as a protein involved in the formation of enamel. By its interaction with FAM83H nuclear CK1 δ is localized to nuclear speckles, which supply splicing factors to active transcription sites (Kuga et al., 2016; Wang et al., 2016). FAM83H contains four Phe-X-X-X-Phe interaction motifs, one of them located in a conserved domain of unknown function (DUF1669). This domain is common to other FAM83 family members as well and interactions with CK1 δ could also be found for FAM83A, FAM83B, and FAM83E (Fulcher et al., 2018). Although FAM83 proteins are substrates for CK1 δ -mediated phosphorylation they are rather considered as regulatory partners directing CK1 isoforms to specific cellular compartments and substrate pools (reviewed in Bozatzi and Sapkota, 2018).

In addition to interaction partners, which have already been mentioned above, numerous additional interacting proteins have been described for CK1 δ within recent years (Table 4). These proteins are not (only) targets for CK1 δ -mediated phosphorylation, but are also involved in more complex regulatory processes and form strong interactions with CK1 δ . Apart from the already mentioned scaffolding protein AKAP450 also the Ran-binding protein in the microtubule-organizing center (MTOC) (RanBPM) was identified as a centrosome-targeted interacting protein for CK1 δ . The proteins interacted in a yeast two-hybrid screen, partially co-localized, and RanBPM was even phosphorylated by CK1 δ (Wolff et al., 2015). Furthermore, interaction between CK1 δ and microtubule-associated protein 1A (MAP1A) has been demonstrated by yeast two-hybrid screen and co-immunoprecipitation. Consequently, microtubule dynamics might be changed *via* CK1 δ -mediated phosphorylation of the light chain LC2 of MAP1A (Wolff et al., 2005). CK1 δ is also involved in the regulation of vesicle transport and synaptic functions, underlined by the fact that CK1 δ interacts with snapin, a protein associated with SNAP25, regulating neurotransmitter release in neuronal cells (Wolff et al., 2006). In developmental processes CK1 δ has been found to interact with the pro-neural basic helix-loop-helix (bHLH) transcription factor Atoh1, which plays a key role in sensory hair development. Following phosphorylation by CK1 δ degradation of Atoh1 is initiated by the E3 ubiquitin ligase Huwe1 (Cheng et al., 2016). As another developmental-associated factor also lymphocyte enhancer factor (LEF-1) can be bound and phosphorylated by CK1 δ , resulting in disruption of binding between LEF-1 and β -catenin while DNA-binding of LEF-1 is not impaired (Hammerlein et al., 2005). Association of CK1 δ has also been reported for the regulatory and complex-building/-initiating molecule 14-3-3 ζ , which also interacts with CK1 α and CK1 ϵ (Dubois et al., 1997; Zemlickova et al., 2004). In order to mediate this interaction

CK1 δ contains the sequence Leu-Gly-Ser-Leu-Pro, which is quite similar to a putative motif described for 14-3-3 binding (Muslin et al., 1996). Finally, almost two decades ago interaction between CK1 δ and the circadian clock proteins PER and cryptochrome (CRY) has been demonstrated by Lee and colleagues. In the circadian cycle CK1 isoforms facilitate the translocation of PERs and CRYs to the nucleus (Lee et al., 2001).

7. CK1 δ -associated cellular functions

7.1. CK1 δ in the circadian rhythm

The circadian rhythm is controlled by the cellular clock, permitting a cellular rhythm of approximately 24 h. Alterations in the circadian rhythm could be observed in different disorders such as sleeping, metabolic, and neurological disorders, which will be discussed in more detail in the following paragraphs (Ferrell and Chiang, 2015; De Lazzari et al., 2018; Leng et al., 2019; Stenvers et al., 2019).

The circadian rhythm is characterized by a negative feedback loop mediated by PER and CRY proteins, whose expression levels oscillate over the circadian clock. PERs and CRYs can form heterodimers, shuttle into the nucleus (Lee et al., 2001; Aryal et al., 2017), and inhibit their own expression through the inhibition of the CLOCK/BMAL1-responsive circadian gene transcription (Virshup et al., 2007). Once in the nucleus, CK1 δ seems to enhance the inhibition of circadian-driven transcription by reducing CLOCK/BMAL1 binding affinity to DNA (Aryal et al., 2017). Since mRNA levels of CK1 δ/ϵ could vary in light-induced phase-shift in mice, CK1 δ/ϵ seems to play an important role in balancing the circadian rhythm (Ishida et al., 2001). In fact, the regulation of PER degradation is mainly influenced by reversible phosphorylation controlled by kinases and phosphatases (so called “phosphoswitch”) (Gallego and Virshup, 2007; Virshup et al., 2007). CK1 δ and ϵ are among the most important kinases, controlling PER phosphorylation (Camacho et al., 2001; Lee et al., 2001; Xu et al., 2005; Narasimamurthy et al., 2018). CK1 δ seems to have a more important and essential role in the circadian clock compared to CK1 ϵ (Etchegaray et al., 2009; Walton et al., 2009). When CK1 δ is disrupted or inactivated, an elongation in the circadian clock has been observed (Etchegaray et al., 2009; Isojima et al., 2009; Lee et al., 2011b; Mieda et al., 2016), while overexpression of CK1 δ leads to a shortening of the circadian rhythm (Lee et al., 2009; Mieda et al., 2016). Inhibition of CK1 δ/ϵ by PF-670462 also has shown inhibitory effects on the expression of clock genes such as *Bmal1*, *Per1*, *Per2* and *Nr1d1* in rats (Kennaway et al., 2015).

After inhibition of N6-methylation (m6A) of CK1 δ mRNA, enhancement of CK1 δ translation permits the expression of CK1 δ TV1 and TV2, which seem to differently influence the circadian rhythm, first by acceleration following increased degradation of PER2 and secondly by deceleration consequently leading to PER2 stabilization (Fustin et al., 2018). Moreover, a recent study identified CK1 δ TV2 with a stronger role in priming phosphorylation of PER2 compared to CK1 δ TV1, which permits subsequent phosphorylation events on PER2 (Narasimamurthy et al., 2018).

Robustness of the circadian clock has been analyzed by Nakajima and colleagues, who confirmed that the inhibition of PER2 phosphorylation by CK1 δ/ϵ leads to destabilization of

the oscillation (Nakajima et al., 2015). Moreover, CK1 δ -mediated phosphorylation of PER2 seems to be a temperature-insensitive process, being responsible for the robustness of this process (Isojima et al., 2009). Nevertheless, the activity of CK1 δ in phosphorylating PER2 seems to be controlled by upstream kinases, likely by cyclin-dependent kinases or proline-directed kinases, which can phosphorylate CK1 δ on Thr-344 or Thr-347, thereby reducing its activity (Ianes et al., 2016; Eng et al., 2017). Interestingly, the circadian rhythm seems to be coupled with – and also be influenced by – the cell cycle (Unsal-Kacmaz et al., 2005). In fact, mutations and deregulation of circadian rhythm components have been observed in cancer (Wood et al., 2008).

7.2. CK1 δ in DNA damage and cellular stress

Stress-conditions, among them genotoxic stress and DNA damage, lead to p53-dependent activation of CK1 δ , finally resulting in CK1 δ -mediated phosphorylation of key regulatory proteins involved in these processes, like p53 and Mdm2 (Knippschild et al., 1997). CK1 δ phosphorylates p53 within its N-terminal domain on residues Ser-4, Ser-6, Ser-9 (Knippschild et al., 1997; Higashimoto et al., 2000), and Ser-20 (MacLaine et al., 2008; Venerando et al., 2010). When p53 is phosphoprimered on Ser-15 additional CK1 δ -mediated phosphorylation on Thr-18 results in lower binding affinity between p53 and Mdm2 and consequently elevated p53 activity (Dumaz et al., 1999; Alsheich-Bartok et al., 2008). Moreover, not only p53 but also its negative regulator Mdm2 can be phosphorylated by CK1 δ . Under normal conditions, CK1 δ -mediated phosphorylation of Mdm2 on Ser-240, Ser-242, Ser-246, and Ser-383 stabilizes the Mdm2-p53 complex and consequently leads to increased degradation of p53 (Blattner et al., 2002; Winter et al., 2004). Interestingly, REG γ (11S regulatory particles, 28-kDa proteasome activator γ) seems to have a role in promoting degradation of CK1 δ , finally leading to stabilization of Mdm2 protein levels and therefore decreased p53 activity (Li et al., 2013). Upon DNA damage, ataxia telangiectasia mutated (ATM)-mediated phosphorylation of CK1 δ leads to phosphorylation of Mdm2, permitting SCF $^{\beta}$ -TrCP (skp cullin F-box containing complex beta-transducin repeat containing protein)-mediated ubiquitination of Mdm2 and its proteasomal degradation (Inuzuka et al., 2010a, Inuzuka et al., 2010b, Wang et al., 2012). Under hypoxia, a hypoxia-inducible factor 1 (HIF-1) heterodimer (HIF-1 α and aryl hydrocarbon receptor nuclear translocator (ARNT)) can form and activate the transcription of hypoxia-responsive genes. CK1 δ plays a role in phosphorylating HIF-1 α on residue Ser-247, thereby interfering with its binding to ARNT and resulting in decreased HIF-1 activity (Kalousi et al., 2010). Interestingly, under hypoxic conditions CK1 δ can also reduce cell proliferation and lipid droplet formation by reducing HIF-1 α /ARNT complex formation (Kourti et al., 2015). The activity of topoisomerase II α (TOPOII- α), another important regulator of DNA replication and cell division, is also influenced by CK1 δ -mediated phosphorylation on residue Ser-1106, finally resulting in increased TOPOII- α function (Grozav et al., 2009). Furthermore, CK1 δ phosphorylates the ubiquitin-like containing PHD and RING finger domains 1 protein (UHRF1), which plays an important role in the maintenance of DNA methylation during DNA replication. Upon DNA damage, enhanced degradation of UHRF1 can be observed due to increased CK1 δ -mediated phosphorylation on Ser-108, permitting binding of the SCF $^{\beta}$ -TrCP E3 ligase and subsequent proteasomal degradation of UHRF1 (Chen et al., 2013).

7.3. CK1δ in cell cycle, mitosis, and meiosis

CK1δ was shown to have important roles in microtubule dynamics, cell cycle progression, genomic stability, mitosis, and meiosis (Behrend et al., 2000a, Behrend et al., 2000b, Sillibourne et al., 2002, Stoter et al., 2005, Johnson et al., 2013, Greer et al., 2014, Penas et al., 2014, Penas et al., 2015, Phadnis et al., 2015, Sakuno and Watanabe, 2015, Chan et al., 2017, Greer et al., 2017). As already mentioned before, CK1δ is anchored to the centrosome *via* its interaction with AKAP450 (Sillibourne et al., 2002), allowing CK1δ-mediated phosphorylation of EB1, a component relevant for centrosome positioning during T cell activation (Zyss et al., 2011). In order to ensure centrosomal integrity and maintenance of genomic stability centrosome-associated CK1δ might also cooperate with a centrosomal subpopulation of p53 (Wahl et al., 1996; Meek, 2000; Tarapore and Fukasawa, 2002). Consequently, CK1δ/ε play an important role in cell cycle progression as well as in genomic stability. Following its inhibition by IC261 cells undergo a transient mitotic arrest (Behrend et al., 2000a), even though additional studies reported that cell cycle arrest upon treatment with IC261 is a result of severe off-target effects mediated by IC261 (Cheong et al., 2011; Stoter et al., 2014). Nevertheless, mouse embryonic fibroblasts (MEFs) lacking CK1δ are characterized by multiple centrosomes and the presence of micronuclei, indicators of genomic instability (Greer et al., 2017). Accordingly, silencing of CK1δ leads to lower amounts of Chk1 and cell division cycle 2 (CDC2)/CDK1, both having important roles in DNA damage response and mitotic checkpoints (Greer et al., 2017). Interestingly, Chk1-mediated regulation of CK1δ as well as their physical binding have previously been shown, confirming interaction of CK1δ with Chk1 (Bischof et al., 2013). Moreover, CK1δ-mediated phosphorylation of Wee1-G2 checkpoint kinase (Wee1) can lead to its proteasomal degradation resulting in increased levels of active CDK1 and the consequent entrance of cells into mitosis (Penas et al., 2014). In line with these results, inhibition of CK1δ or its destruction after APC/CCdh1 (adenomatous polyposis coli/cyclosome cadherine 1)-mediated ubiquitination increases the stability of Wee1 kinase, which elevates CDK1 phosphorylation, leading to cell cycle exit (Penas et al., 2014; Penas et al., 2015). On the other hand, CK1δ is also able to phosphorylate phosphoprime septation initiation protein 4 (Sid4), thereby initiating the recruitment of Chk2/Cds1 (checkpoint kinase 2/replication checkpoint kinase Cds1) and a subsequent mitotic commitment (Chan et al., 2017). On the other hand, under mitotic stress, Hhp1 and Hhp2 (Hhp1/2), orthologous forms of CK1 in *Schizosaccharomyces pombe*, have been identified to play an important role in the mitotic checkpoint by delaying cytokinesis. By co-localization with spindle pole bodies (SPBs), CK1 can phosphorylate Sid4, thereby inducing Dma1-mediated ubiquitination and degradation of Sid4, leading to cytokinesis suspension (Johnson et al., 2013; Elmore et al., 2018). Inhibition of CK1 isoforms by D4476 also increases the mitotic cell rate *via* increased stability of β-catenin and elevated β-catenin-mediated transcription, confirming an important role of CK1 in mitosis and cell cycle progression (Benham-Pyle et al., 2016).

Apart from its involvement in mitosis CK1δ also plays an important role in the regulation of meiotic processes. CK1δ and its ortholog Hrr25 have been detected within P-bodies, cytoplasmic RNA-protein granules present in meiotic cells. This binding seems to reduce CK1 turnover into the cytoplasm, thereby preserving protein integrity for subsequent stages of meiosis (Zhang et al., 2016; Zhang et al., 2018). Localization of Hrr25 to P-bodies is

necessary for completion of the meiotic program (Zhang et al., 2018). Hrr25 has also been observed to be involved in the induction of nuclear division of meiosis as well as in the synthesis of membranes to engulf newly synthesized nuclei, thereby mediating the exit from meiosis II (Arguello-Miranda et al., 2017). In oocytes in metaphase I and in metaphase II CK1 δ co-localizes with γ -tubulin at the spindle poles (Qi et al., 2015). However, CK1 δ seems not to be essential for spindle organization and meiotic progression in human cells. This is in contrast to earlier studies performed in yeast. Ishiguro and colleagues showed that Hhp2, the CK1 δ /e ortholog in *S. pombe*, acts as cohesion kinase promoting cleavage of the cohesion subunit Rec8 (meiotic recombination protein Rec8) during meiosis (Ishiguro et al., 2010; Katis et al., 2010). This observation is supported by a report from Rumpf and colleagues showing that the CK1 δ /e orthologs Hhp1 and Hhp2 in *S. pombe* are essential to achieve full phosphorylation of Rec8 and subsequent efficient removal of Rec8 during meiosis I (Rumpf et al., 2010). This data impressively shows that results based on investigations in yeast models cannot necessarily be transferred to mammalian cells. However, stromal antigen 3 (STAG3), the mammalian ortholog of meiotic recombination protein Rec11, is also phosphorylated by CK1, thereby confirming the conservation of this process and the observations made in yeast, showing that Rec11 is phosphorylated by Hhp1 and Hhp2, subsequently permitting DNA breakage and consequent meiotic recombination (Phadnis et al., 2015; Sakuno and Watanabe, 2015).

7.4. CK1 δ -specific functions associated with cytoskeleton components

Numerous studies report cellular localization of CK1 δ to components of the cytoskeleton, where CK1 δ exercises essential regulatory tasks: CK1 δ is able to modulate microtubule polymerization and stability at the spindle apparatus and the mitotic centrosome by directly phosphorylating α -, β -, and γ -tubulin (Behrend et al., 2000b; Stoter et al., 2005). Not only tubulin itself, but also microtubule-associated proteins (MAPs) are interacting with – and are phosphorylated by CK1 δ , subsequently resulting in modulated interaction of MAPs with microtubules and altered microtubule dynamics (Brouhard and Rice, 2018). So far, site-specific phosphorylation by CK1 δ has been demonstrated for MAP4, MAP1A, and tau, as well as for the microtubule-destabilizing protein stathmin (Behrend et al., 2000b; Li et al., 2004; Wolff et al., 2005; Hanger et al., 2007; Leon-Espinosa et al., 2013). Microtubule nucleation at the Golgi apparatus was inhibited by siRNA-mediated knock-down of CK1 δ . Furthermore, the localization of CK1 δ to the centrosome plays a crucial role in ciliogenesis: based on a study specifically knocking-down CK1 δ kinase activity (by either using a CK1 δ -specific inhibitor or specific siRNA) CK1 δ has been shown to mediate primary ciliogenesis by interaction with AKAP450 proteins as well as by maintaining Golgi organization and directed protein trafficking (Greer et al., 2014). This is supported by another study suggesting a role for CK1 δ in the assembly of primary cilia (Lee et al., 2012). In contrast, the same study impressively showed an involvement of the highly related isoform CK1 ϵ in a Wnt5a-CK1 ϵ -Dvl2-Plk1-mediated pathway for cilia disassembly.

Ciliogenesis in general can be linked to the activity of distinct cellular signal transduction pathways. By compartmentalization of essential signal molecules the cilium has been shown to restrain signaling *via* the canonical Wnt as well as the Hedgehog (Hh) pathway (Rohatgi et al., 2007; Corbit et al., 2008; Lancaster et al., 2011). Furthermore, ciliogenesis can be

promoted by activity of the Hippo pathway (Kim et al., 2014). In conclusion, with its role in direct regulation of ciliogenesis, CK1 δ might not only be able to directly modulate the activity of the Wnt, Hh, and Hippo pathways (see chapters below), but also to indirectly control their activity by regulating (dis-)assembly of the primary cilium as a physical signal transduction platform used by the mentioned pathways.

7.5. CK1 δ in the Wnt pathway

The Wnt signaling pathway plays an important role in developmental processes, regeneration, cell proliferation and tissue homeostasis. In many types of cancers alterations or mutations in the Wnt pathway have been observed (Clevers and Nusse, 2012; Polakis, 2012; Nusse and Clevers, 2017; Krishnamurthy and Kurzrock, 2018). Briefly, in absence of Wnt ligand, β -catenin is phosphorylated and ubiquitinated by the β -catenin destruction complex, leading to its proteasomal degradation. Upon Wnt binding to Frizzled (Fzd), the co-receptor LRP5/6 can be phosphorylated by CK1 α and glycogen synthase kinase 3 (GSK3). Subsequently, Axin binds to LRP5/6 and recruits the β -catenin destruction complex, permitting higher stability of β -catenin. β -catenin shuttles into the nucleus, associates with TCF transcription factor, and induces the transcription of Wnt target genes (Clevers and Nusse, 2012; Nusse and Clevers, 2017).

As previously summarized in different focused review articles, CK1 isoforms are involved in different ways in the Wnt signaling pathway (Cruciat, 2014; Knippschild et al., 2014; Price, 2006). CK1 δ has been shown to phosphorylate the Wnt pathway components Dishevelled 1 (Dvl1) as well as Axin, APC, and β -catenin (Amit et al., 2002; Gao et al., 2002; Xing et al., 2003; Ha et al., 2004). Accordingly, CK1 δ was also observed to have an essential role in neurite formation and dopaminergic neuron differentiation by phosphorylating Dvl (Bryja et al., 2007; Greer and Rubin, 2011). Moreover, CK1 δ/ϵ phosphorylate Dvl2, thereby playing an important role for intestinal stem cell (ISC) maintenance. In fact, co-ablation of CK1 δ and ϵ leads to the elimination of ISCs (Morgenstern et al., 2017). In addition, CK1 δ seems to be important for the regulation of planar cell polarity (PCP), which depends on proper phosphorylation of planar cell polarity protein Van Gogh-like 2 (Vangl2), mediated by CK1 δ/ϵ following Wnt-5a-mediated induction of the non-canonical Wnt signaling pathway (Yang et al., 2017).

CK1 δ can either (i) positively or (ii) negatively influence the Wnt pathway: (i) CK1 δ can stabilize β -catenin after the phosphorylation of lipoprotein receptor-related protein 6 (LRP6) and the subsequent recruitment of Axin and the β -catenin destruction complex, thereby avoiding β -catenin phosphorylation and ubiquitination (Zeng et al., 2005; Wu et al., 2009). Moreover, CK1 δ/ϵ activity as well as stability are influenced by the tumor promoter TPA (12-O-tetra-decanoylphorbol-13-acetate), which also permits increased binding of β -catenin to TCF4E in a CK1 δ/ϵ -dependent manner, resulting in an activation of Wnt target genes (Su et al., 2018). (ii) CK1 δ negatively influences the Wnt pathway by directly phosphorylating β -catenin on Ser-45, thereby priming β -catenin for further GSK3 β -mediated phosphorylation and subsequent degradation (Amit et al., 2002).

7.6. CK1 δ in the Hedgehog pathway

The Hedgehog (Hh) signaling pathway plays an important role in embryonic development by regulating cell differentiation, regeneration, proliferation, and organogenesis. Deregulation and mutations of main players of this pathway can influence tumorigenesis and cancer development (Jiang and Hui, 2008; Yao and Chuang, 2015; Wu et al., 2017). Briefly, in absence of Hh ligand (Sonic Hedgehog (Shh), Indian hedgehog (Ihh), or Desert hedgehog (Dhh)) the twelve-pass-membrane receptor Patched (Ptch) inhibits the seven-pass membrane receptor Smoothened (Smo). In this context, cubitus interruptus/glioma-associated oncogene (Ci/Gli) transcription factor can be phosphorylated, undergoes partial proteasomal degradation, and shuttles into the nucleus where it can act as a repressor of Hh-targeted gene transcription. Once Hh binds to Ptch, Smo receptor can be phosphorylated and Ci/Gli transcription factor can migrate into the nucleus to activate Hh target genes (Jiang and Hui, 2008; Heretsch et al., 2010; Wu et al., 2017). CK1 isoforms play different roles in the Hh pathway. CK1 δ has recently been shown to increase Smo activity by phosphorylating Smo at Ser-683 after priming phosphorylation mediated by PKC (Jiang et al., 2014). Upon Hh stimulation, CK1 δ phosphorylates the full-length Cubitus interruptus positive transcription factor (CiA), protecting it from proteasomal degradation (Shi et al., 2014). In contrast, site-specific phosphorylation of Ci by CK1 results in enhanced binding of SCF^{Slimb} E3 ubiquitin ligase to Ci, subsequently leading to proteasomal degradation of Ci (Smelkinson et al., 2007). Additionally, after priming phosphorylation by PKA, CK1 phosphorylates CiA, thereby increasing its proteolysis and generation of the repressive form of Ci (CiR) (Price and Kalderon, 2002).

7.7. CK1 δ in the Hippo pathway

The Hippo pathway is involved in embryonic development to determine organ size by influencing cell proliferation, apoptosis, and tissue homeostasis (Zeng and Hong, 2008; Bae and Luo, 2018; Moon et al., 2018). Hippo signaling is activated by high cell density. A phosphorylation cascade is induced after phosphorylation of mammalian sterile-20 like kinase 1/2 (MST1/2), which further phosphorylates large tumor suppressor kinase 1/2 (LATS1/2), ultimately phosphorylating yes-associated protein (YAP)/tafazzin (TAZ). As major downstream target YAP/TAZ can either be ubiquitinated and degraded or retained in the cytoplasm after binding to 14-3-3. Under conditions of low cell density, the Hippo-signaling cascade is not activated and YAP/TAZ is able to translocate into the nucleus and to bind TEAD (TEA domain)/SMAD (SMA/mothers against decapentaplegic) transcription factors, inducing Hippo target gene transcription for growth and differentiation (Zeng and Hong, 2008, Bae and Luo, 2018, Moon et al., 2018). YAP degradation is also influenced by CK1 δ -mediated phosphorylation on Ser-381, after its priming phosphorylation by LATS on Ser-127, which permits the recruitment of the E3 ubiquitin ligase SCF ^{β -TrCP}, ubiquitination, and subsequent degradation of LATS (Zhao et al., 2010). Interestingly, the Hippo pathway seems to be connected to the Wnt pathway in different ways, for instance by interaction of YAP/TAZ with DVL, β -catenin, and the β -catenin destruction complex (Varelas et al., 2010; Heallen et al., 2011; Azzolin et al., 2012; Imajo et al., 2012; Rosenbluh et al., 2012; Konsavage Jr. and Yochum, 2013; Azzolin et al., 2014; Wang et al., 2018), as well as with regulation of p53 (Ferraiuolo et al., 2017; Furth et al., 2018). Hippo signaling can negatively influence Wnt signaling *via* Dvl protein, which in presence of Wnt ligand

binding is phosphorylated by CK1 δ /e and inhibits the β -catenin destruction complex. In this context, YAP/TAZ binds Dvl, thereby reducing its CK1 δ /e-mediated phosphorylation as well as the subsequent transduction of Wnt signaling (Varelas et al., 2010; Imajo et al., 2012). Moreover, phosphorylated YAP/TAZ is able to bind β -catenin, which is then retained in the cytoplasm, resulting in a decreased transcription of Wnt target genes (Heallen et al., 2011; Imajo et al., 2012). Interestingly, YAP/TAZ have also been identified as downstream effectors of the non-canonical Wnt signaling pathway, whose target genes seem to have inhibitory potential on canonical Wnt signaling (Park et al., 2015).

8. Involvement of CK1 δ in pathological processes

Most studies in regard to the involvement of CK1 δ in the development and progression of certain diseases and disorders concentrate on the relation of CK1 δ to cancer and neurologic diseases. Apart from those, also disorders affecting cell cycle, metabolism, and stem cell functions associated with CK1 δ are another main topic. Furthermore, metabolic diseases as well as inflammatory and infectious diseases related to CK1 δ -specific functions are also reported in some studies and will be discussed in the following sections.

8.1. CK1 δ in tumorigenesis and tumor progression

Cancer-associated functions of CK1 δ are closely related to the above described roles of CK1 δ in Wnt/ β -catenin-, p53-, Hh-, and Hippo-related signaling. Meanwhile numerous studies described the oncogenic features of CK1 δ in different types of cancer. These include, among others, gastrointestinal tumors, breast cancer, kidney cancer, hematological malignancies, and skin cancer. A database research analyzing microarray datasets generated from the analysis of certain tumor cell lines and tumor tissues revealed that CK1 δ mRNA is overexpressed in many cancer types like bladder cancer, brain cancer, breast cancer, colorectal cancer, kidney cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, and prostate cancer, as well as in hematopoietic malignancies (Fig. 8 and Table 5) (Schitteck and Sinnberg, 2014).

Animal experiments and cell culture-based analysis confirmed increased expression of CK1 δ in cells of hyperplastic B cell follicles and B cell lymphoma in p53-deficient mice, but also in choriocarcinoma cells and pancreatic ductal adenocarcinoma (Maritzen et al., 2003; Stoter et al., 2005; Brockschmidt et al., 2008). The function of CK1 δ in lymphoid neoplasms was first described using a mouse model leading to the observation that the expression level of CK1 δ is increased in cells of hyperplastic B follicles and advanced B cell lymphomas in p53-deficient mice. Later, CK1 δ mRNA and protein levels were also analyzed in 18 lymphoma cell lines and strong expression of CK1 δ could be found in all analyzed cell lines (Maritzen et al., 2003; Winkler et al., 2015).

Interestingly, in some other studies low expression of CK1 δ in cancer tissues has also been described (Fig. 8 and Table 5). Decreased expression levels of CK1 δ may result in cell cycle arrest and apoptosis in various cancer cell lines. These effects are independent of Wnt/ β -catenin-mediated signal transduction. However, they seem to depend on activation of RAS and inactivation of p53 (Cheong et al., 2011; Cheong and Virshup, 2011). Decreased activity of CK1 δ has also been characterized in SV40-transformed cells *in vitro* and in SV40-

induced mammary carcinogenesis in a bitransgenic mouse model *in vivo*. In this model CK1δ kinase activity is impaired by site-specific mutations (*e.g.* N172D) and transgenic, mutant CK1δ exercises a dominant-negative effect on endogenous CK1δ. The resulting partial inhibition of CK1δ activity reduced transformation of SV40-transformed cells, decelerated tumor progression, and prolonged survival of WAP-mutCK1δ/WAP-T bitransgenic mice (Hirner et al., 2012). In contrast, the R324H mutation in the C-terminal region of CK1δ is associated with increased oncogenic potential and results in promotion of the development of adenomas in the intestinal mucosa (Tsai et al., 2007). Furthermore, the T67S mutant identified in colorectal cancer tissue exhibits increased kinase activity also resulting in higher oncogenic potential. Overexpression of CK1δ^{T67S} leads to enhanced colony formation of HT29 cells and increased tumor formation in xenografts (Richter et al., 2015).

Studies on the analysis of a correlation of CK1δ and the overall survival of cancer patients revealed that high expression levels of CK1δ are associated with shorter patient survival in glioblastoma, lung cancer, and colorectal cancer patients (Schitteck and Sinnberg, 2014; Richter et al., 2016). In contrast, a high expression of CK1δ with longer patient survival time can be found in breast cancer, chronic lymphocytic leukemia, and astrocytic glioma patients (Schitteck and Sinnberg, 2014).

8.2. Neurologic diseases and disorders

Immunohistochemistry and gene expression studies have demonstrated that CK1 isoforms are expressed to a different extend in various parts of the nervous tissue (Schwab et al., 2000; Camacho et al., 2001; Yasojima et al., 2001; Chergui et al., 2005; Lohler et al., 2009). Other studies have been conducted to examine the relationship of CK1δ in brain tissue to specific pathological hallmarks by immunohistochemistry. Those studies found that CK1δ is associated with the corresponding specific pathological hallmarks of Alzheimer's disease (AD), Down syndrome (DS), progressive supranuclear palsy (PSP), parkinsonism dementia complex of Guam (PDC), Pick's disease (PiD), pallido-ponto-nigral degeneration (PPND) (Schwab et al., 2000), and familial advanced sleep phase syndrome (FASPS) (Xu et al., 2005; Ebisawa, 2007).

Alzheimer's disease is a progressive neurodegenerative disease characterized by two specific brain lesions. One lesion is described by the appearance of neurofibrillary tangles (NFTs), abnormal neurites, known as neuropil threads, and neuritic plaques (NPs) in nerve cells (Buee et al., 2000). The second lesion is represented by granulovacuolar degeneration bodies (GVBs) formed in the hippocampus (Okamoto et al., 1991). Filaments of accumulated microtubule-associated tau protein can be considered as reliable marker for neurofibrillary degeneration (Flament et al., 1990). Localization analysis of CK1δ in pathological tissue of patients with Alzheimer's disease revealed that the highest expression levels of CK1δ in pathological tissues can be detected in GVBs, and the second highest levels were detected in NPs. Low CK1δ expression levels could be detected in NFTs. In addition, hippocampal expression levels of CK1δ in Alzheimer's patients were higher than in the control group. Interestingly, analysis of expression levels of CK1δ in different organs of AD patients revealed that elevated levels of CK1δ could only be found in the brain but not in peripheral

organs. In brain tissue, the expression levels of CK1δ are remarkably increased in brain areas with increased tau pathology, while the expression levels of CK1δ are modestly elevated in areas with low NFT burden (Yasojima et al., 2000). Moreover, co-localization studies confirmed that CK1δ is co-localized with its interaction and substrate protein tau in the specific pathological tissue lesions like NFTs or GVBs (Schwab et al., 2000).

Typically, NFTs are composed of aggregated filaments formed by hyperphosphorylated tau. Tau can be phosphorylated by CK1δ at Ser-202, Thr-205, Ser-396, and Ser-404 *in vitro*. Furthermore, exogenous expression of CK1δ in HEK293 cells induced tau phosphorylation and resulted in reduced binding of tau to microtubules (Li et al., 2004). Mass spectrometry-based analysis of tau phosphorylation revealed that CK1δ and GSK3β are responsible for phosphorylation of most sites detected in hyperphosphorylated tau protein and that CK1δ together with GSK3β might play an important role in the pathogenesis of AD (Hanger et al., 2007). Therefore, CK1δ could be a potential target for AD treatment and recently, different inhibitors have been developed and may be therapeutically useful in the future. Interestingly, [¹¹C]-labeled CK1 inhibitors have been developed as derivatives of already published difluoro-dioxolo-benzoimidazol-benzamide compounds (Richter et al., 2014), and have been used as radiotracers for CK1 in positron emission tomography (PET) imaging for both, diagnosis and therapeutic follow up (Gao et al., 2018). TDP-43 (transactive response DNA-binding protein of 43 kDa) has been characterized as a hallmark of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) (Amador-Ortiz et al., 2007; Bigio, 2011). Moreover, some studies have also shown that TDP-43 is deposited in GVBs and can also be strongly associated with the clinical phenotype of AD. Here, TDP-43 contributes to the AD neurodegenerative process through beta-amyloid (Aβ)-dependent and Aβ-independent pathways (Chang et al., 2016). The relationship between CK1δ and TDP-43 is first reflected in their localization to GVBs. Moreover, by studying different stages of granulovacuolar degeneration the increased distribution areas of TDP-43 in brain lesions were found to be consistent with the distribution of CK1δ (Thal et al., 2011). In ALS, phosphorylation of TDP-43 by CK1δ has been indicated *in vitro* and by liquid chromatography-ion trap mass spectrometry (LC-MS/MS), thereby identifying 29 sites within TDP-43 being targeted by CK1δ (Kametani et al., 2009). TDP-43 intracellular accumulation and mislocalization seems to be influenced by CK1δ-mediated phosphorylation (Nonaka et al., 2016). Accordingly, inhibition of CK1δ-mediated phosphorylation of TDP-43 by different CK1δ inhibitors in a neuronal cell model as well as in a *Drosophila* model resulted in prevention of neurotoxicity and rescue of cells from cell death (Alquezar et al., 2016). Recently, a newly developed CK1δ inhibitor (IGS3.27) could also reduce phosphorylation of TDP-43 and additionally led to normalization of TDP-43 translocation (Posa et al., 2018). Therefore, CK1δ seems to be an interesting target of inhibition for ALS therapy concepts and a lot of effort has been made to improve CK1δ-selectivity as well as permeability of CK1δ-specific inhibitors through the blood-brain-barrier (BBB) (Alquezar et al., 2016; Joshi et al., 2016; Wager et al., 2017). Interestingly, the FDA-approved drug riluzole, which is already used as a clinical treatment for ALS, can inhibit CK1δ/ε, even though with a quite high half maximal inhibitory concentration (IC₅₀) value (~16 μM) (Bissaro et al., 2018).

CK1 δ is also involved in Parkinson's disease (PD) as indicated by its ability to phosphorylate α -synuclein, one of the main component of Lewy bodies (LB), on Ser-87 and Ser-129 (Okochi et al., 2000). However, priming phosphorylation of α -synuclein on Tyr-125 seems to be necessary for CK1 δ -mediated phosphorylation on Ser-129 (Kosten et al., 2014). Different mutations of α -synuclein have been characterized in PD, among them E46K, which seems to enhance Ser-129 phosphorylation (Mbefo et al., 2015).

Familial advanced sleep phase syndrome (FASPS) is a circadian rhythm sleeping disorder (CRSD) characterized by very early sleep onset and offset, as well as by a short τ period (the period in which behavior continues to oscillate in the absence of external cues) (Jones et al., 1999). The mammalian clock protein PER2 plays a key role in the regulation of circadian rhythms in FASPS. Etiology studies carried out by screening patients' genes detected a missense mutation (T44A) in the PER2-binding domain of human CK1 δ or a S662G mutation in the clock gene *PER2* to be causative for FASPS (Xu et al., 2005; Xu et al., 2007). Introduction of human CK1 δ T44A changed the circadian rhythm in both, transgenic *Drosophila* and transgenic mice. However, only changes observed in the mouse model were similar to the shortened circadian period observed in human. Changes observed in transgenic *Drosophila* were associated with a lengthened circadian period (Xu et al., 2005). A subsequently performed study confirmed *in vivo* phosphorylation of PER2 by CK1 δ at Ser-662. Following site-specific phosphorylation of PER2 at Ser-662 the protein is characterized by increased stability and longer half-life compared to non-phosphorylated PER2 (Shanware et al., 2011). Hyeong-Min Lee and colleagues could show that orchestrated action of CK1 δ and protein phosphatase 1 (PP1) can determine cell circadian periodicity thorough their influence on PER phosphorylation state. In CK1 δ /e-deficient fibroblasts, PER phosphorylation was significantly reduced and cell rhythm disappeared. In contrast, inhibition of PP1 is able to induce high phosphorylation levels of PER resulting in shortened cell rhythm (Lee et al., 2011a). Furthermore, different multi-phosphorylation site mutants of CK1 δ were characterized to have different activity on PER2 stability, while the most significant impact on PER2 stability was observed for the CK1 δ T347A mutant. These results indicate that PER2 stability can be influenced by site-specific phosphorylation of CK1 δ at Thr-347, performed by other intracellular kinases (Eng et al., 2017).

8.3. CK1 δ in the mediation of drug addiction

Via modulation of the circadian rhythm-regulating PER proteins or the dopaminoceptive signal integrator dopamine and cAMP-regulated neuronal phosphoprotein 32 (DARPP-32), CK1 δ (but also CK1 ϵ) can be involved in the development of drug addiction (Nairn et al., 2004; Falcon and McClung, 2009). Certain mutations in the gene coding for PER2 proteins have previously been linked to conditioned place preference (CPP) of cocaine and increased alcohol consumption, highlighting the role of PER2 in the development of addictive behavior (Abarca et al., 2002; Spanagel et al., 2005). Using the CK1 δ /e-specific inhibitor PF-670462 relapse-like alcohol consumption in rats could successfully be prevented by centrally mediated modulation of PER2 phosphorylation (Perreau-Lenz et al., 2012).

The neurotransmission integrator protein DARPP-32 is involved in mediating the motoric and rewarding effects of drugs like heroin (Fernandez et al., 2006; Mahajan et al., 2009).

Following activation of dopamine D1 receptors by heroin PKA-mediated phosphorylation of DARPP-32 is induced, finally leading to inhibition of PP1 by phosphorylated DARPP-32 and subsequent increase in drug-related rewarding properties (Fernandez et al., 2006). In this pathway CK1 δ and ϵ can be involved by phosphorylating DARPP-32 at Ser-130, resulting in increased phosphorylation of Thr-34 by PKA and subsequent DARPP-32/PP1 signaling (Nairn et al., 2004; Svenningsson et al., 2005). Also here, treatment with the CK1 δ / ϵ -specific inhibitor PF-670462 attenuated methamphetamine-induced locomotor activity by inhibition of DARPP-32 phosphorylation mediated by CK1 δ and ϵ (Bryant et al., 2009). Furthermore, treatment with the highly potent CK1 δ / ϵ -specific inhibitor PF-5006739 resulted in attenuation of drug-seeking behavior in rats trained to self-administer the synthetic opioid fentanyl (Wager et al., 2014). In conclusion, specific inhibitors of CK1 δ (and ϵ) might be of future use for the treatment of drug addiction or alcohol abuse.

8.4. Metabolic diseases

Apart from sleeping disorders also the onset and severity of metabolic diseases, including obesity and type 2 diabetes, can be linked to circadian clock disorders. Therefore, as a key regulator of the circadian clock, CK1 δ can also affect metabolic dysfunction and can serve as promising drug target. In this context, glucose tolerance was improved by daily administration of a CK1 δ - (and ϵ -)specific inhibitor (PF-5006739) to mice in a model for diet-induced obesity or in a genetic mouse model for obesity (ob/ob) (Cunningham et al., 2016). CK1 δ can furthermore be linked to circadian metabolic regulation *via* PGC-1 α (peroxisome proliferator-activated receptor γ co-activator 1 α), a transcriptional coactivator coordinating circadian metabolic rhythms by simultaneously regulating the expression of metabolic and clock genes. Phosphorylation of PGC-1 α by CK1 δ enhances its proteasomal degradation, thereby inhibiting the transcriptional function of PGC-1 α in cultured hepatocytes, resulting in decreased gluconeogenesis gene expression and glucose secretion (Li et al., 2011b). In contrast to this observation, the treatment of a human adipocyte cell line with CK1 δ -specific inhibitors resulted in increased basal and insulin-stimulated glucose uptake (Xu et al., 2015). Xu and colleagues reported that the expression of adiponectin, an important adipokine secreted by adipose tissue, was associated with CK1 δ expression in adipose tissue of morbidly obese patients. Furthermore, *in vitro* studies revealed that Ser-174 and Thr-235 of adiponectin are phosphorylated by CK1 δ *in vitro*, contributing to modulation of the ability of adiponectin to form biologically active high molecular complexes (Xu et al., 2015).

8.5. Hijacking of mammalian CK1 pathways by CK1s from parasites

There is increasing evidence suggesting that CK1 is associated with infectious diseases by the manipulation of host cell CK1 signaling pathways by intracellular parasites, mediated through the export of their own CK1 into the host cell (Sacerdoti-Sierra and Jaffe, 1997; Silverman et al., 2010a; Silverman et al., 2010b; Dorin-Semlat et al., 2015; Jiang et al., 2018). Their survival depends on their ability to subvert the host cell to acquire nutrients or to evade the immune response (Lamotte et al., 2017). For instance, *Leishmania* resides in the parasitophorous vacuole of macrophages from where it modifies macrophage biology and attenuates the immune response (Lamotte et al., 2017). *Plasmodium* infects red blood cells (RBCs), and modifies their cell membrane to favor the adhesion of the infected RBCs to the

vascular endothelium and thus avoid clearance by the spleen (Zhang et al., 2015b). In these two parasites, CK1 has been shown to be excreted and could thus contribute to the reprogramming of the respective host cells (Sacerdoti-Sierra and Jaffe, 1997; Silverman et al., 2010a; Dorin-Semlat et al., 2015). The identified host functions of parasitic CK1s imply that these kinases could replace mammalian CK1s to ensure similar functions, including phosphorylation of human CK1 substrates and regulation of human CK1 signaling pathways (Liu et al., 2009). The BLAST and reverse BLAST of the parasitic CK1s with human CK1 shows that they are closely related to human CK1 (see Supplementary Fig. 2 for alignment). More specifically, these kinases display a higher level of identity toward human CK1δ TV1, suggesting that they might be preferentially hijacking the functions of this paralog. The protein sequences of these orthologs is absolutely conserved within each different species for *Trypanosoma brucei*, *Trypanosoma cruzi*, *Plasmodium*, and *Leishmania* (Rachidi et al., 2014). This finding suggests that there is a strong evolutionary selection pressure to maintain the protein sequence unchanged and as closely related to its human counterpart as possible.

The protein organization of parasitic CK1s is very similar to that of human CK1δ. Indeed, all the residues involved in ATP binding, the gatekeeper (Met-82), the DFG, the KHD, and the SIN motifs, as already defined in Fig. 5, are conserved, suggesting that they are crucial for CK1 function. In contrast, other motifs like the CLS are less conserved. The glycine-rich ATP binding loop is conserved in all the selected CK1 sequences, except for TcCK1. The amino acid substitution present in TcCK1 does not affect ATP binding as those residues are conserved, but instead its potential regulation is affected. Indeed, the GSGSFG domain is replaced by GAGSFG in TcCK1. However, in *Leishmania* CK1.2, the two serines of this motif are phosphorylated during differentiation, suggesting that they could have a regulatory effect for LmCK1.2 ((Tsigankov et al., 2014) and own unpublished data); in *Trypanosoma brucei*, *Plasmodium falciparum*, and in *Toxoplasma gondii*, the first serine of the motif is phosphorylated (Nett et al., 2009; Treeck et al., 2011). However, despite phosphorylation of the glycine triad during differentiation, it has been shown that LmCK1.2 is still active, although its activity is lower after differentiation (Rachidi et al., 2014). The catalytic loop motif represents a domain for which a *T. cruzi*-specific substitution has been identified. In all parasitic CK1s except for *T. cruzi* the motif DVKPDN (present in human CK1δ) is replaced by the motif DIKPDN, which is similar to that of human CK1α. In *T. cruzi* CK1 the human motif is replaced by the motif DMKPDN. These changes could be important, as they seem to be conserved. Altogether, these findings indicate that parasitic CK1s are closely related to CK1δ, but additionally have characteristics of CK1α and CK1ε.

However, still very little is known about the functions of these kinases in the parasites and more importantly about their functions in the host cell. The most studied CK1s are that of *Plasmodium* and *Leishmania*:

Plasmodium falciparum has only one CK1, PfCK1 (PF3D7_1136500), which presents 69% of identity with human CK1 in the kinase domain (Barik et al., 1997). PfCK1 was shown to be essential for completion of the asexual intra-erythrocytic cycle (Solyakov et al., 2011). It is expressed throughout blood stage, localizes in the parasite but also in the host red blood cell, especially associated to the surface of the RBC during the first step of infection (Dorin-

Semblat et al., 2015). Indeed, data from Magowan et al. suggests that PfCK1 could be phosphorylating protein 4.1 and the mature-parasite-infected erythrocyte surface antigen (MESA), two components of the erythrocyte membrane skeleton (Magowan et al., 1998). Moreover it has been shown to be secreted in the culture medium. This finding suggests that PfCK1 could be involved in priming other RBCs for subsequent invasion (Dorin-Semblat et al., 2015). A study of the PfCK1 interactome indicates that, similarly to other CK1s, it has multiple binding partners and thus regulates multiple pathways, including transcription, translation, and protein trafficking. Finally, PfCK1 function is likely to be essential for parasite proliferation in erythrocytes.

Leishmania donovani has six CK1 paralogs. Two paralogs, LdBPK_351020.1 and LdBPK_351030.1 (LmCK1.2), are closely related (67% identity), but mainly differ within their C-terminal domains (Martel et al., 2017). They display the highest identity to human CK1. Recently, Martel et al. showed that LdBPK_351020.1 is not essential for parasite survival and could have a role during stationary phase (Martel et al., 2017). The four other paralogs, LdBPK_303530.1, LdBPK_251640.1, LdBPK_041230.1, and LdBPK_271680.1, are extremely divergent from the first two (Rachidi et al., 2014). Little is known about the functions of the six paralogs, except for LdBPK_271680.1, which contains an excretion signal and is important for regulating growth of cultured parasites and virulence (Dan-Goor et al., 2013), and LdBPK_351030.1, which is the most abundant CK1 in *Leishmania* and the only paralog described as having a function in the host cell (Rachidi et al., 2014; Silverman et al., 2010a). LdBPK_351030.1 (LmCK1.2) is active in both, promastigotes and amastigotes, and can be inhibited by D4476, a CK1-specific inhibitor (Rachidi et al., 2014). LmCK1.2 seems to have been selected for its capacity to interact with and phosphorylate host proteins to modulate macrophage-mediated processes to favor the survival of the parasite. Four pieces of evidence support this hypothesis: (i) LmCK1.2 is released into extracellular compartments inside vesicles (Silverman et al., 2010a), (ii) LmCK1.2 is strictly conserved between *Leishmania* species and closely related to human CK1 δ , (iii) *Leishmania* CK1 phosphorylates human interferon alpha/beta receptor 1 (IFNAR1), which leads to the attenuation of the cellular response to interferon alpha (Liu et al., 2009), and (iv) LmCK1.2 is essential for *Leishmania* intracellular survival in the mammalian host. Little is known about the functions of LmCK1.2 in the parasite, as only few substrates have been found, among them heat shock proteins 90 and 70 (Hsp90 and Hsp70), and no interaction partners ((Hombach-Barrigah et al., 2019) and Martel et al., manuscript in preparation). LmCK1.2 is sensitive to known human CK1 inhibitors and is inhibited by CKI-7, IC261, and D4476 (Rachidi et al., 2014). Interestingly, results obtained for IC261 (IC₅₀ of 10 μ M for LmCK1.2 versus 4.8 μ M for mammalian CK1) suggest that the ATP binding pocket of LmCK1.2 might be structurally closer to that of CK1 α than to that of CK1 δ (Rachidi et al., 2014). As *Leishmania* CK1 is essential for parasite survival in the macrophage, it constitutes a perfect target for anti-leishmanial therapy. Several screens looking for small molecules able to inhibit LmCK1.2 and thus kill the parasites were performed and despite the high identity to human CK1, small molecules were identified to more specifically target *Leishmania* CK1 (Allocco et al., 2006; Marhadour et al., 2012; Durieu et al., 2016).

Altogether, by being exported into the host cells, parasitic CK1s take over functions normally performed by human CK1. Studying these orthologs could bring more knowledge

on the functions of human CK1s and lead to new therapeutic strategies preventing hijacking of the host cell by parasites.

9. Modulating CK1δ activity

Recently, interest in modulating the activity of CK1δ has increased enormously. The main focus is directed to the development of highly effective small molecule inhibitors (SMIs) since deregulation of CK1δ expression and activity levels contributes to the pathogenesis of severe disorders, among them cancer and neurologic diseases like AD, PD, ALS, and sleeping disorders. However, due to the existence of several highly conserved CK1 isoforms (CK1α, γ₁₋₃, δ, ε) with overlapping or opposed physiological and pathophysiological functions, it is very challenging to design SMIs being selective for CK1δ only. Furthermore, there is increasing evidence that posttranslational modifications of CK1δ, especially site-specific phosphorylation within its C-terminal regulatory domain, modulates the efficiency of SMIs (Bischof et al., 2012; Bischof et al., 2013; Richter et al., 2014). It is also very challenging and of high clinical interest to develop SMIs with higher affinity toward CK1δ mutants with increased oncogenic potential since their use would expand the therapeutic window and decrease the occurrence of severe side effects enormously.

Within the last 30 years more and more CK1-specific SMIs have been developed. Since most of the compounds described so far are classified as ATP-competitive inhibitors (type I inhibitors), it cannot be excluded that due to structural similarities within the ATP binding site additional kinases and other ATP binding proteins are also inhibited to some extent.

Whereas the first CK1 inhibitor, CKI-7 (N-(2-aminoethyl)-5-chloroisoquinoline-8-sulfonamide), did not show any CK1 isoform-specificity (Chijiwa et al., 1989), IC261 (3-[(2,4,6-trimethoxyphenyl)-methylidene]-indolin-2-one) (Mashhoon et al., 2000) and D4476 (4-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-pyridin-2-yl-1H-imidazol-2-yl]-benzamide) (Rena et al., 2004) exhibit a higher selectivity toward CK1δ and ε. Although CK1δ/ε-specific inhibition by IC261 affects site-specific phosphorylation of Bid and induces apoptosis in tumor cells (Izeradjene et al., 2004), several cellular effects of IC261 are not due to inhibition of CK1δ/ε. Among these effects are the inhibition of microtubule polymerization, which is due to the direct binding of IC261 to tubulin (Cheong et al., 2011; Stoter et al., 2014), and the blocking of voltage-gated sodium channels, which are implicated in tumor progression (Fohr et al., 2017). Furthermore, due to the fact that many CK1-specific inhibitor compounds are classified as ATP-competitive inhibitors (type I inhibitors) comparison of their efficacy is difficult since their IC₅₀ values have been assessed at different ATP concentrations (Supplementary Table 1) (reviewed in Knippschild et al., 2014).

Several structure-based virtual screens resulted in the identification of various CK1δ-specific inhibitors, among them amino-anthraquinone analogues (Cozza et al., 2008), N6-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,6-diamine derivatives (Yang et al., 2012), and the dihydroxyquinoline sulphonamide NSC45572 (Myrianthopoulos et al., 2017). A group-based quantitative structure and activity relationship (QSAR) model based on N-benzothiazolyl-2-phenyl acetamide derivatives (Salado et al., 2014) was generated by Joshi

and co-workers. Using this model, site-specific molecular fragments of individual compounds allow for the interpretation of observed differences in the biological activity of these compounds. Compounds identified using this approach could be used as lead substances against CK1 δ , able to block CK1 δ -mediated site-specific phosphorylation of TDP-43 and might be useful for developing new therapeutic concepts for the treatment of ALS (Joshi et al., 2016).

In addition, several benzimidazole-based CK1-specific inhibitors have demonstrated their potential to specifically inhibit CK1 δ and ϵ (SR-3029 and SR-2890 (Bibian et al., 2013); Bischof-5 and Bischof-6 (Bischof et al., 2012); Richter-2 (Richter et al., 2014); IWP-2, IWP-4, and compound 19 (Garcia-Reyes et al., 2018)). Although Bischof-5, a 2-benzamido-N-(1H-benzo[d]imidazol-2-yl)thiazole-4-carboxamide derivative with a trifluoromethyl substitution on the phenyl ring, exhibits IC₅₀ values toward rat CK1 δ and human CK1 δ transcription variants 1 and 2 between 22 and 42 nM, its ability to inhibit proliferation of various tumor cell lines is limited (Bischof et al., 2012). However, the specificity, activity, and anti-proliferative activity has further been increased by a difluoromethyldioxolo group on the benzimidazole, finally leading to the development of Richter-2 (IC₅₀ CK1 δ = 0.14 μ M vs. IC₅₀ CK1 ϵ = 0.52 μ M (Richter et al., 2014)).

Optimization of benzimidazole derivatives by Bibian and coworkers included enhancement of the interaction of compounds with Arg-13 of CK1 δ , thereby reducing off-target effects by altering the substituents on the benzimidazole unit (either R1 or R2) and increasing inhibition of CK1 δ , which could be achieved by using piperazine or *N*-methyl piperazine as R4 and thiophene, furan, and 3-fluorophenyl groups as R3. These modifications finally resulted in development of the highly CK1 δ / ϵ -selective inhibitors SR-2890 and SR-3029 with improved inhibitory and anti-proliferative features (Bibian et al., 2013).

Interestingly, due to structural similarities to benzimidazole-based CK1 inhibitors, especially to Bischof-5 (Bischof et al., 2012), inhibitors of Wnt production (IWPs), known to be antagonists of the Wnt pathway by preventing Wnt ligand palmitoylation through inhibition of the membrane-bound O-acyltransferase porcupine (Porcn), have recently been described to specifically inhibit CK1 δ . This led to the development of improved IWP-based ATP-competitive inhibitors of CK1 δ and to the conclusion that the effects observed for IWPs are not only due to Porcn inhibition, but also to effects on CK1 δ / ϵ -related signaling (Garcia-Reyes et al., 2018).

Quite recently, [¹¹C] labeled highly potent difluoro-dioxolo-benzimidazol-benzamides have been generated, which have a high potential to be prognostically used as PET radiotracers for imaging of AD (Gao et al., 2018).

Several additional small molecule inhibitors, which have been described to exhibit dual specificity, will be introduced in the following paragraph. Compound (*R*)-DFR053 ((*R*)-2-(1-hydroxybut-2-ylamino)-6-[3-(2-pyridyl)phenylamino]-9-isopropylpurine), a roscovitine derivative, specifically targets CK1 δ and CDK5, and could be useful for the analysis of pathways involved in neurodegeneration and therapeutic applications in AD (Oumata et al., 2008). The pyrazolo-pyridine analogues MRT00055778 (N1-[4-(5-methyl-3-

phenylisoxazol-4-yl]pyrimidin-2-yl]acetamide) and MRT00033659 (5-(3-acetamidophenyl)-3-methyl-1H-pyrazolo[3,4-*b*]pyridine) have been shown to inhibit CK1δ and Chk1, finally resulting in stabilization of the p53 pathway (Huart et al., 2013). In addition, the Clk-specific inhibitor TG003, a benzothiazole derivative (Muraki et al., 2004), has been described to inhibit Clk and CK1 isoforms in a mouse model for mechanical allodynia and thermal hyperalgesia (Kurihara et al., 2014). Based on structural similarity between N-(benzo[*d*]thiazol-2-yl)-2-phenylacetamide derivatives with CK1 inhibitory activity and 1-(benzo[*d*]thiazol-2-yl)-3-phenylureas which have been designed as Aβ-binding alcohol dehydrogenase (ABAD) inhibitors, several benzothiazolylphenylureas could be identified as dual-specific inhibitors, among them K690 and K691, presenting an interesting class of dual-specific anti-AD therapeutics (Benek et al., 2018).

Several diaryl-isoxazoles and -imidazoles have been described as dual inhibitors against p38α MAPK and CK1δ/ε. Whereas PF-670462 (4-[3-cyclohexyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-pyrimidin-2-ylamine) possesses only poor CK1 isoform selectivity compound PF-4800567 exhibits a much stronger inhibition of CK1ε than CK1δ (Badura et al., 2007; Walton et al., 2009).

Seerden and colleagues could demonstrate structure-activity relationship of 4-(40-fluorophenyl)imidazoles as specific inhibitors of p38α MAPK, CK1δ, or JAK2 with IC₅₀ values lower than 100 nM (Seerden et al., 2014).

In addition, substituted isoxazoles 1 and 2 with the typical vicinal pyridin-4-yl/4-*F*-phenyl pharmacophore (Peifer et al., 2009), which have been originally generated and characterized as ATP-competitive inhibitors for p38α MAPK (IC₅₀ p38α MAPK 1 = 0.45 μM and p38α MAPK 2 = 2.2 μM) (Peifer et al., 2007; Peifer et al., 2008), exhibited significant inhibition of CK1δ at 10 μM. Molecular modeling of compound 1 resulted in an optimizing strategy to develop (E)-3-(2,4-dimethoxy-phenyl)-N-(4-[5-(4-fluoro-phenyl)-2-methylsulfanyl-3H-imidazol-4-yl]-pyridin-2-yl)-acrylamide (compound 17) and (E)-3-(2,4-dimethoxy-phenyl)-N-(4-[5-(4-fluoro-phenyl)-2-methanesulfinyl-3H-imidazol-4-yl]-pyridin-2-yl)-acrylamide (compound 18) as dual-specific inhibitors with high selectivity toward CK1δ at an ATP concentration of 100 μM (compound 17: IC₅₀ p38α MAPK = 19 nM, IC₅₀ CK1δ = 4 nM, IC₅₀ CK1ε = 73 nM; compound 18: IC₅₀ p38α MAPK = 41 nM, IC₅₀ CK1δ = 5 nM, IC₅₀ CK1ε = 447 nM) (Peifer et al., 2009).

Recently, 3-(2,5-dimethoxyphenyl)-N-(4-(5-(4-fluorophenyl)-2-(methylthio)-1H-imidazol-4-yl)-pyridin-2-yl)-propanamide (compound 11b) and 4-(2,5-dimethoxyphenyl)-N-(4-(5-(4-fluorophenyl)-2-(methylthio)-1H-imidazol-4-yl)-pyridin-2-yl)-1-methyl-1H-pyrrole-2-carboxamide (compound 16b) have been developed with high specificity toward CK1δ (compound 11b: IC₅₀ CK1δ = 4 nM, IC₅₀ CK1ε = 25 nM, IC₅₀ p38α MAPK = 10 nM), 16b (IC₅₀ CK1δ = 8 nM, IC₅₀ CK1ε = 81 nM, p38α MAPK = 10 nM) and remarkable efficacy for inhibiting the growth of various pancreatic tumor cell lines (Halekotte et al., 2017).

In order to develop a CK1δ/ε-specific inhibitor able to cross the blood-brain-barrier (BBB) structure-based drug design resulted in synthesis of PF-5006739 (4-{4-(4-fluorophenyl)-1-[1-(1,2-oxazol-3-ylmethyl)piperidin-4-yl]-1H-imidazol-5-yl}pyrimidin-2-

amine), exhibiting an IC₅₀ value of 3.9 nM for CK1δ and 7 nM for CK1ε and showing centrally mediated delay of the circadian rhythm in animal models (Wager et al., 2014).

Furthermore, N-(1H-pyrazol-3-yl)-quinazolin-4-amines have been developed to specifically inhibit CK1δ/ε. Compounds 3c and 3d exhibited good binding interactions with CK1δ/ε and could therefore serve for optimizing their ability to specifically inhibit CK1δ/ε (Karthikeyan et al., 2017).

Finally, natural products with inhibitory activity against CK1δ/ε, like chloromethylhalicyclamine B, isolated from the marine sponge *Acanthostrongylophora ingens*, allow for the development of highly active CK1δ/ε-specific inhibitors, structurally different to the inhibitors known so far (Esposito et al., 2016).

Since SMIs often exhibit low bioavailability, off-target effects, and severe side effects, there are only some reports demonstrating biological activity of CK1δ-specific inhibitors in animal models (Table 6). Therefore, interest in identification and validation of synthetic peptides able to inhibit CK1δ kinase activity or to block the interaction of CK1δ with cellular proteins has increased remarkably.

In this context a peptide library based on the amino acid sequences of human CK1δ TV1 and 2 was recently used to determine the dominant contacts of the interaction surface between α-tubulin and CK1δ. Peptide P39 (also named peptide δ-361 = peptide sequence starting at CK1δ amino acid 361) showed the strongest interaction with GST-α-tubulin. Furthermore, binding of δ-361 to α-tubulin also resulted in selective inhibition of CK1δ-mediated phosphorylation of GST-α-tubulin, whereas phosphorylation of α-casein was not affected. In cells, δ-361 is able to disturb the CK1δ/α-tubulin interaction, finally leading to microtubule destabilization and cell death (Kruger et al., 2016).

Previously, interaction of CK1 isoforms with the DEAD-box RNA helicase DDX3X has been reported to result in stimulation of CK1 kinase activity and Wnt signaling (Cruciat et al., 2013). Moreover, Wnt-associated mutations of DDX3X can be associated with medulloblastoma. Using a CK1δ/ε-derived peptide library to fine-map the interaction domains for DDX3X on CK1δ and ε, several CK1δ- or ε-derived peptides were identified being able to interact with DDX3X, among them peptides δ-1, δ-41, ε-1, and ε-41. Furthermore, *in vitro* kinase reactions revealed the ability of peptides δ-1, δ-41, and ε-41 (but not ε-1) to block the activation of CK1δ/ε by DDX3X, probably due to inhibition of the activating interaction of DDX3X with CK1δ/ε. Furthermore, peptides δ-1, δ-41, and ε-41 were able to inhibit stimulation of CK1 kinase activity in cell culture. Considering that mutations in DDX3X identified in medulloblastoma patients increase the activity of CK1 in living cells, leading to aberrant stimulation of CK1-mediated pathways, such as Wnt/β-catenin and Hh signaling, the identified interaction-blocking peptides could provide a powerful tool for new therapeutic therapy concepts for the treatment of Wnt/β-catenin- or Hh-driven cancers (Dolde et al., 2018).

Recently, a peptide microarray was also used for mapping the interaction regions within intrinsically disordered regions of human Axin 1, a scaffolding protein playing central roles in Wnt signaling. The interaction domains necessary for Axin 1 to interact with CK1δ/ε

were identified and it could be shown that Axin 1 and Dvl compete for CK1 δ /e-mediated site-specific phosphorylation thereby pointing to an important role of Axin 1 in modulating phosphorylation of Dvl by CK1 δ /e and activation of the canonical Wnt pathway (Harnos et al., 2018).

While selective inhibition of CK1 δ is desired in the case of cancer or neurodegenerative disease, in the context of regenerative processes also activation of CK1 kinase activity could be of therapeutic benefit. For instance, kinase activity of CK1 δ and e has been shown to be essential in a model for neuronal regeneration (Bischof et al., 2011). However, no small molecule-based activators of CK1 δ have been available so far, and while promising results have initially been published reporting the activation of CK1 α by the small molecule pyrvinium (Thorne et al., 2010) a later performed study disproved the described effects. Instead of directly activating CK1 α pyrvinium mediates its effects *via* a complex mechanism involving down-regulation of PKB/Akt and activation of GSK3 (Venerando et al., 2013).

10. Concluding remarks

Numerous studies mainly performed within the last two decades provide strong evidence demonstrating that CK1 isoform δ is a key player in several cellular signal transduction pathways. Consequently, if control mechanisms regulating expression and activity of CK1 δ are rendered ineffective, dysregulation of CK1 δ can contribute to the pathogenesis of certain diseases. Due to this reason numerous CK1-specific small molecule inhibitors have been developed in recent years. Although the development of CK1 isoform-specific inhibitors remains a major challenge to the scientific community, some compounds already showed promising results in cell culture- and animal-based studies analyzing efficacy *e.g.* for the treatment of cancer or neurodegenerative diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

A	alanine
aa	amino acids
ABAD	A β -binding alcohol dehydrogenase
AD	Alzheimer's disease
AIB1	amplified in breast cancer 1
AKAP	A-kinase anchor protein
ALS	amyotrophic lateral sclerosis
APC	adenomatous polyposis coli
APC/C Cdh1	anaphase-promoting complex/cyclosome in complex with activator protein CDH1
ARF GAP1	ADP-ribosylation factor GTPase-activating protein
Arg or R	arginine
ARNT	aryl hydrocarbon receptor nuclear translocator
Asn or N	asparagine
Asp or D	aspartic acid
ATM	ataxia telangiectasia mutated
Atoh1	proneural basic helix-loop-helix (bHLH) transcription factor
ATP	adenosine triphosphate
Aβ	beta-amyloid
BACE1	β -secretase
BBB	blood-brain-barrier
bHLH	basic helix-loop-helix
BLAST	basic local alignment search tool
BLOC-1	biogenesis of lysosome-related organelles complex-1
BMAL1	Brain and Muscle ARNT-Like 1
BYSL	bystin-like protein
CAT	catalytical

CCdh1	cyclosomecadherin1
CDC	cell division cycle
CDK	cyclin-dependent kinase
CG-NAP	Golgi N-kinase anchoring protein
Chk1	checkpoint kinase 1
Chk2/Cds1	checkpoint kinase 2/replication checkpoint kinase Cds1
Ci	cubitus interruptus
Ci-155	full-length cubitus interruptus
CiA	cubitus interruptus positive transcription factor
CiR	cubitus interruptus repressive transcription factor
CK1BP	casein kinase 1 binding protein
CK1α/γ1–3/δ/ϵ	casein kinase 1 alpha/gamma 1–3/delta/epsilon
CKL2	CDC-like kinase 2
CLL	chronic lymphocytic leukemia
C-lobe	C-terminal lobe
CLS	centrosome localization signal
CPI-17	protein kinase C-potentiated myosin phosphatase inhibitor of 17 kDa
CPP	conditioned place preference
CREB	cyclic AMP response element-binding protein
CRY	cryptochrome
CSNK1D	casein kinase 1 delt
C-terminus	carboxy-terminus
Cx43	connexin-43
Cys or C	cysteine
DARPP-32	dopamine and cAMP-regulated neuronal phosphoprotein 32
dCK	deoxycytidine kinase
DD	dimerization domain
DDX3X	DEAD-box RNA helicase 3 X-linked

Dhh	desert hedgehog
Dma1	E3 ubiquitin-protein ligase Dma1
Dnmt1	DNA methyltransferase 1
DPC	dystrophin-associated protein complex
Dpr1a	dapper1a
DS	Down syndrome
DUF1669	domain of unknown function 1669
Dvl	dishevelled
EB1	microtubule plus-end-binding protein 1
eIF6/Tif6p49	eukaryotic initiation factor 6
Emi2	endogenous meiotic inhibitor 2
ENP1	essential nuclear protein 1
ePK	eukaryotic protein kinase
ERα	estrogen receptor α
FAM83	family with sequence similarity 83
FASPS	familial advanced sleep phase syndrome
FoxG1	forkhead box G1
FTLD	frontotemporal lobar degeneration
Fzd	frizzled
Gli	glioma-associated oncogene
Gln	glutamine
Glu	glutamic acid
Gly or G	glycine
GSK3β	glycogen synthase kinase 3β
GST	glutathione S-transferase
GVBs	granulovacuolar degeneration bodys
Hh	hedgehog
HIF-1α	hypoxiainducible factor 1α
hnRNP A1	heterogeneous nuclear ribo-nucleoprotein A1

HPI	hydrophobic pocket I
HRII	hydrophobic region II
Hsp90/70	heat shock protein 90/70
HTP	high-throughput
Huwe1	E3 ubiquitin-protein ligase Huwe1
IC₅₀	half maximal inhibitory concentration
ICP0	human herpes virus (HHV) E3 ubiquitin ligase
IFNAR1	interferon alpha/beta receptor 1
Ihh	Indian hedgehog
IKK	inhibitor of κ B (I κ B) kinase
Ile or I	isoleucine
ISC	intestinal stem cell
IWP	inhibitor of Wnt production
k_{cat}	catalyst rate constant
KD	kinase domain
KHD	kinesin homology domain
K_m	Michaelis constant
LATS1/2	large tumor suppressor kinase 1/2
LEF-1	lymphocyte enhancer factor-1
Leu or L	leucine
LRP	lipoprotein receptor-related protein
LTP	low-throughput
Lys or K	lysine
M	molar
m6A	N6-methylation
Mam1	Monopolin complex subunit Mam1
MAP	microtubule-associated protein
MAPK	mitogen activated protein kinase
MAPT	microtubule-associated protein tau

MBP	myelin basic protein
MBP	myelin basic protein
MDM2	murine double minute 2 homolog
MEF	mouse embryonic fibroblast
Met or M	methionine
MESA	mature-parasite-infected erythrocyte surface antigen
mGluR	group I metabotropic glutamate receptor
MST1/2	mammal sterile-20 like kinase 1/2
mTNFα	transmembrane tumor necrosis factor α
MTOC	microtubule-organizing center
MTSS1	metastasis suppressor 1
NEDD4	neural precursor cell expressed developmentally down-regulated protein 4
NFAT1	nuclear factor of activated T-cells 1
NFTs	neurofibrillary tangles
N-lobe	N-terminal lobe
NLS	nuclear localization signal
nm23-H1	nucleoside diphosphate kinase A
Nop56	nucleolar protein 56
NPs	neuritic plaques
N-terminus	amino-terminus
p53	tumor protein 53
P-bodies	processing bodies
PCP	planar cell polarity
PD	Parkinson's disease
PDB	protein data bank
PDC	parkinsonism dementia complex of Guam
PET	positron emission tomography
PER	period circadian protein homolog

PGC-1α	proliferator-activated receptor γ co-activator 1 α
Phe or F	phenylalanine
PiD	Pick's disease
PKA	protein kinase A
PKB/Akt	protein kinase B
PKCa	protein kinase C alpha
PKD2	protein kinase D2
Plk1	polo-like kinase 1
Porcn	porcupine
PP1	protein phosphatase 1
PPND	pallido-ponto-nigral degeneration
ppUL44	human cytomegalovirus phosphoprotein
Pro or P	proline
PS-2	presenilin-2
pSer	phospho-serine
PSP	progressive supranuclear palsy
Ptch	patched
pThr	phospho-threonine
RanBPM	Ran-binding protein in the microtubule-organizing center (MTOC)
RBC	red blood cell
Rec11	meiotic recombination protein Rec11
Rec8	meiotic recombination protein Rec8
REGγ	11S regulatory particles, 28-kDa proteasome activator γ
RhoA	Ras homolog family member A
RPL4/8/13	ribosomal protein L4/8/13
SCF	skp cullin F-box containing complex
SCS	sulfatide and cholesterol-3-sulfate
Ser or S	serine

Shh	sonic Hedgehog (Shh)
Sid4	septation initiation protein sid4
Sid4	septation initiation protein Sid4
SMAD	SMA/mothers against decapentaplegic
SMI	small molecule inhibitor
Smo	smoothened
SNAP25	synaptosomal nerve-associated protein 25
SPBs	spindle pole bodies
SPRY2	sprouty2
Sre1N	yeast sterol regulatory element-binding protein homolog
SRR-1	sensitivity to red light reduced 1
STAG3	stromal antigen 3
SV2A	synaptic vesicle protein 2A
SV40 T-Ag	simian virus 40 large T-antigen
SV40	simian virus 40
Swi6	chromatin-associated protein swi6
TAZ	tafazzin
TDP-43	TAR DNA-binding protein of 43 kDa
TEAD	TEA domain
TGN	trans Golgi network
Thr or T	threonine
TOP2A	topoisomerase II α
TOPOII-α	topoisomerase II α
TPA	12-O-tetradecanoylphorbol-13-acetate
TV	transcription variant
Tyr or Y	tyrosine
UHRF1	ubiquitin-like containing PHD and RING finger domains 1 protein
UVB	ultraviolet B radiation

Val	valine
Vangl2	planar cell polarity protein Van Gogh-like 2
V_{max}	maximum enzyme reaction velocity
Wee1	Wee1 G2 checkpoint kinase
Wnt	Wingless/Int-1
X	any amino acid
Y	any amino acid except serine or threonine
YAP	yes-associated protein
β-TrCP	beta-transducin repeat containing protein

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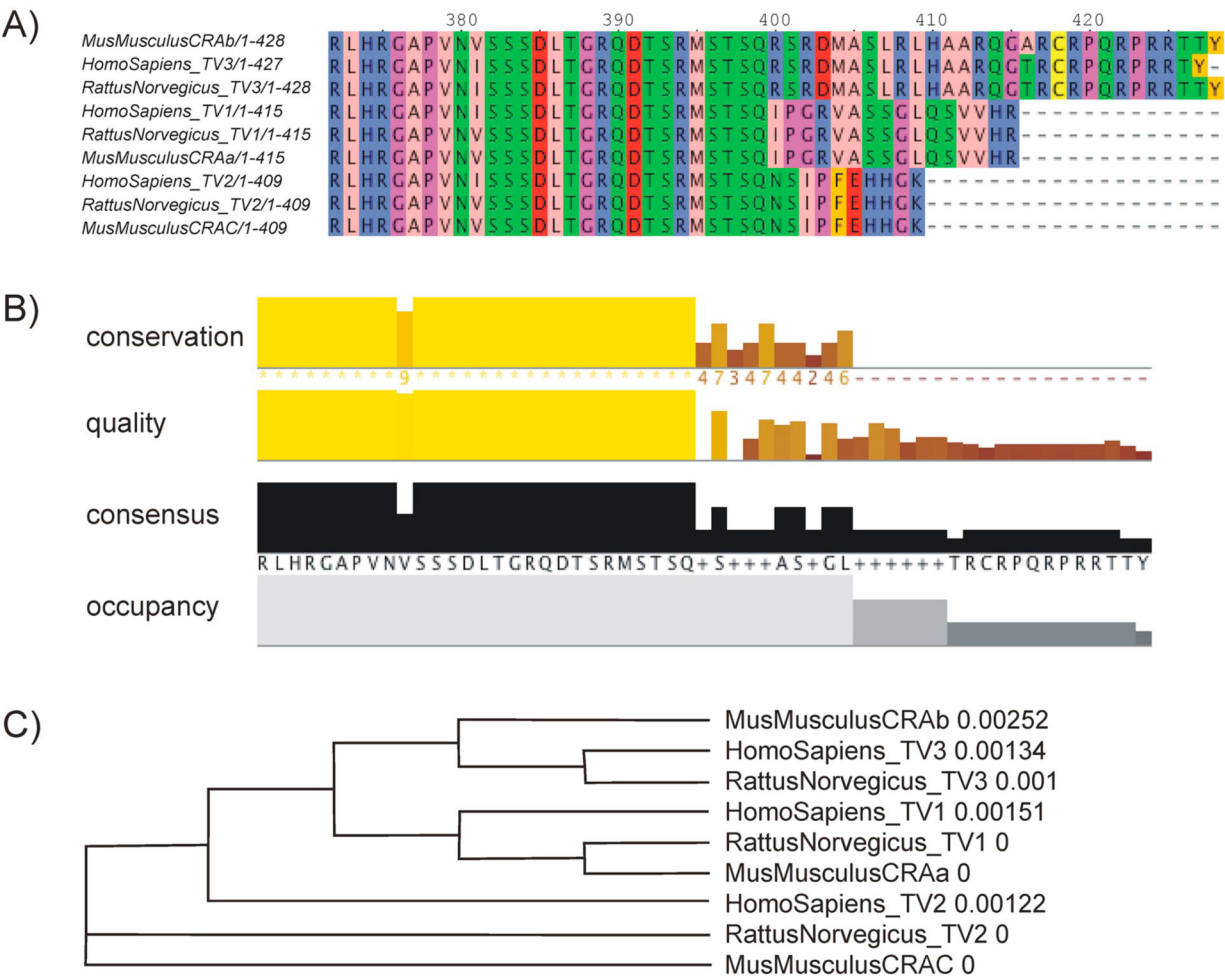


Fig. 1. Comparison of the amino acid sequences of three different CK16 sequences in human, rat, and mouse. The alignment presented in (A) is followed by a display of the conserved regions, the quality, the consensus sequence as well as the occupancy of the alignment. The conservation as well as the quality is displayed with a color code ranging from yellow (highly conserved, good quality) to brown (poorly conserved, poor quality) (B). Alignments presented in panels A and B are shown starting from amino acid 372. The sequences are also displayed in a phylogenetic tree, indicating the relationship between the various CK16 variants. The alignments as well as the phylogenetic tree were generated using the alignment information from the Clustal Omega algorithm (Madeira et al., 2019) (C). TV, transcription variant.

Exon [bp]	1	2	3	4	5	6	7	8	9	10	11
TV1	455	101	149	229	171	149	172	140	-	2171	-
TV2	455	101	149	229	171	149	172	140	64	2171	-
TV3	455	101	149	229	171	149	172	140	-	-	1044

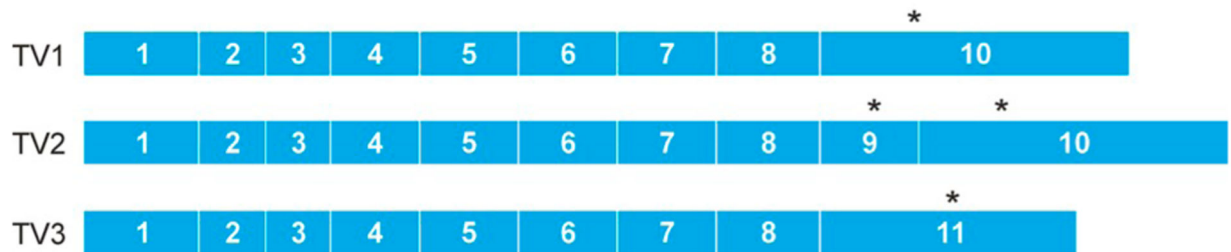
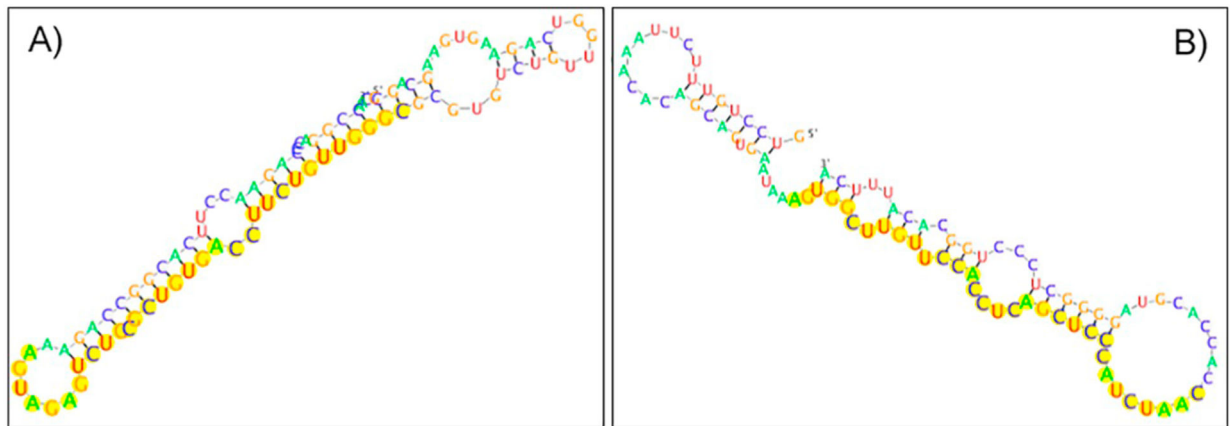


Fig. 2.

Exon structure of the three transcription variants of CK18 in humans. The stop codon position of each variant is marked with the asterisk. The information of TV1, TV2, and TV3 can be found using the data bank NCBI (GI: 13097702, 16041786, and 1393428169). Bp, base pairs; TV transcription variant.

**Fig. 3.**

Predicted RNA folding structure of the polyadenylation motif and the flanking regions of TV1 and TV2 on exon 10 (A) as well as TV3 on exon 11 (B). The minimum free energy values for TV1/TV2 and TV3 are -28.70 kcal/mol and -16.03 kcal/mol, respectively. This might indicate that TV1 and TV2 are less polyadenylated compared to TV3 based on the observation that stable secondary structures decrease the polyadenylation of the specific site (Klasens et al., 1998).

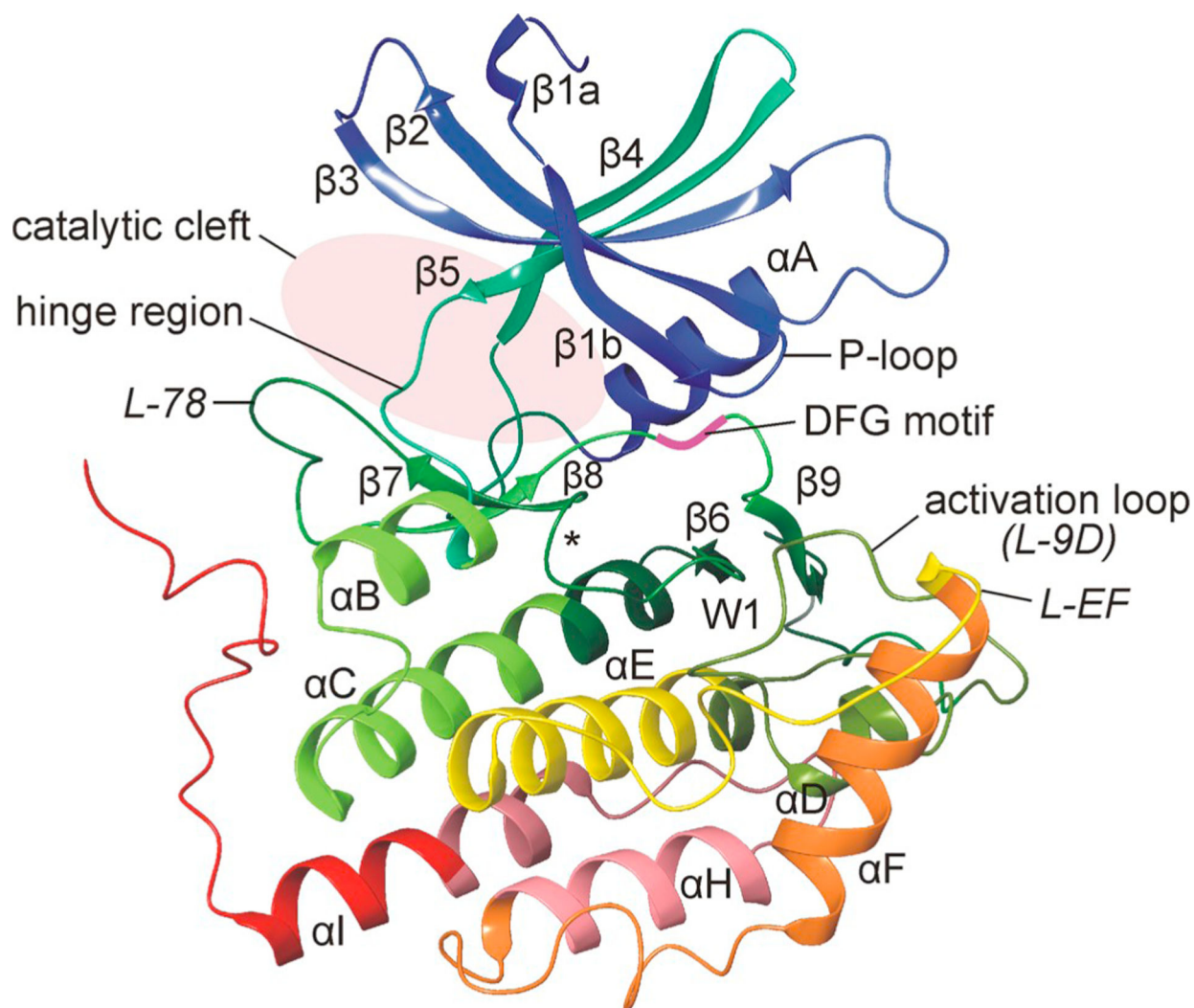
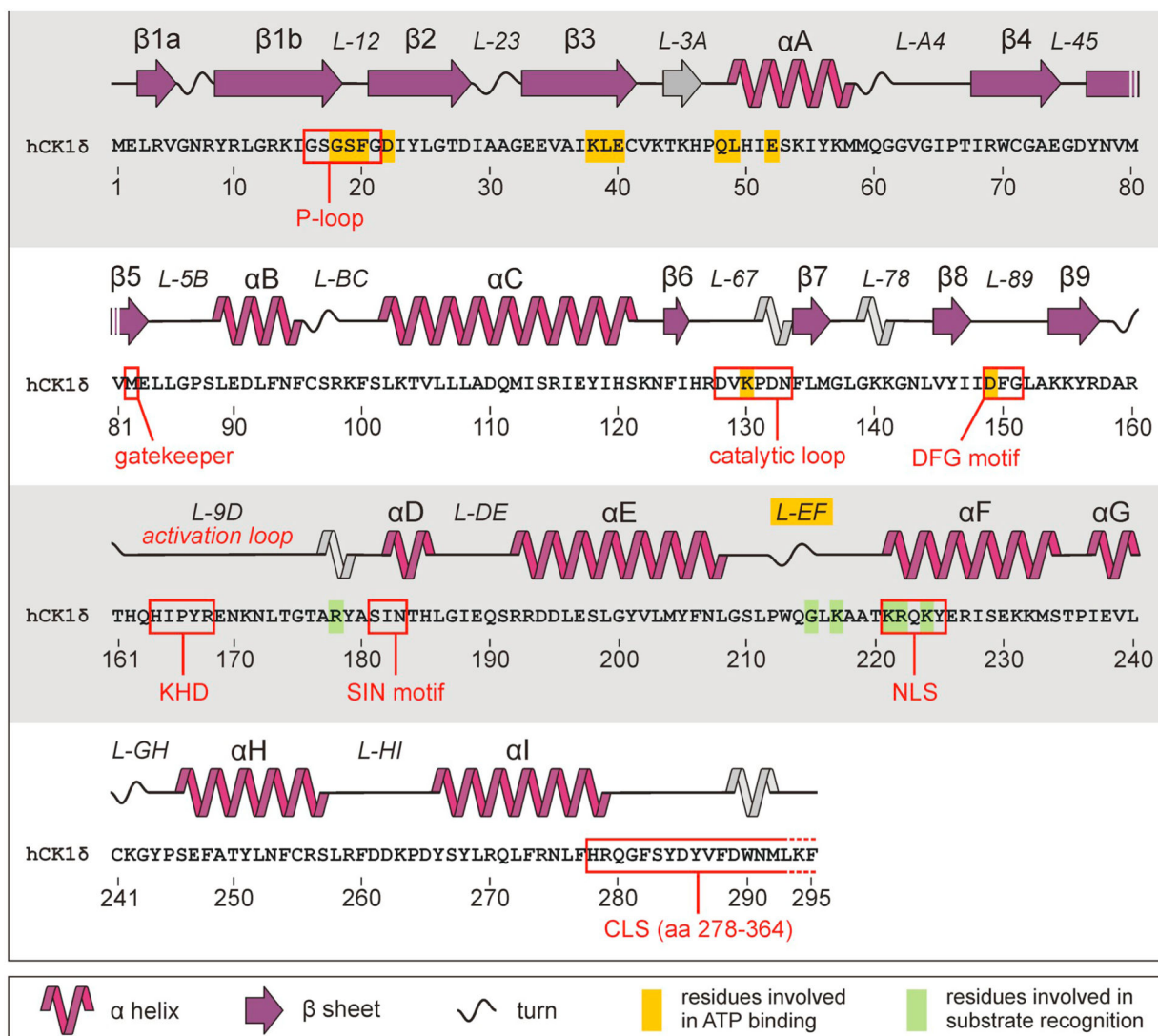


Fig. 4. Three-dimensional structure of human CK1δ. Representation of the three-dimensional structure of human CK1δ. The structure of the N-lobe mainly consists of β -sheet strands while the larger C-terminal lobe is mainly composed by α -helices and loop structures. Structural elements are labeled according to Xu et al. (1995). Domains and residues of functional importance are labeled accordingly. Within loop L-89 the DFG motif is located with its aspartate residue being crucial for kinase activity and enzymatic function. Identification of a tungstate binding domain, indicated by W1, led to the identification of a recognition motif for the binding of phosphorylated substrates. The position of the catalytic loop (L-67) is marked with the asterisk (Xu et al., 1995; Longenecker et al., 1996). The figure was created by using CK1δ crystallization data deposited in the protein data bank (PDB) with ID 6GZM (Minzel et al., 2018).

**Fig. 5.**

Detailed representation of secondary structure, functional domains, and functional amino acid residues in the kinase domain of human CK1δ. Localization of structural elements building the CK1δ kinase domain is shown for α-helices, β-sheets, turns, and loop-structures. Nomenclature of elements is indicated as first published by Xu et al. (1995). Structures not described in the initial publication are shown in grey. Domains of functional importance are marked with red boxes while amino acid residues involved in ATP binding or substrate recognition are marked with yellow or green background, respectively. Because human CK1δ TV1, 2, and 3 are fully conserved in the N-terminal domain and the kinase domain, the depicted protein sequence is representative for all three variants. Unfortunately, data regarding three-dimensional structure of the C-terminal domain is not available. CLS, centrosome localization signal; KHD, kinesin homology domain; NLS, nuclear localization signal; TV, transcription variant.

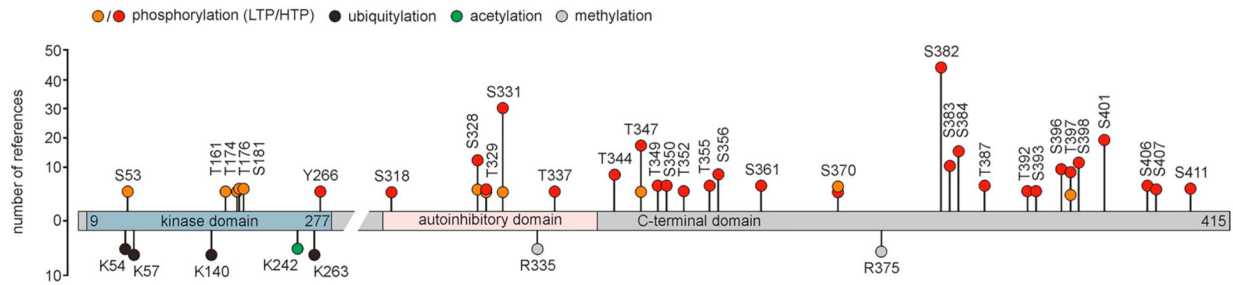


Fig. 6.

Posttranslational modification of human CK1δ. Identified posttranslational modifications of CK1δ TV1 are indicated at their reported positions. Because most modifications have been reported for the C-terminal domain, this domain is depicted in a stretched presentation compared to the kinase domain. In the case of phosphorylation the distinction is made between reports of low-throughput studies and high-throughput studies. The figure was created based on information provided for CK1δ by PhosphoSitePlus® (Hornbeck et al., 2015). HTP, high-throughput studies, LTP, low-throughput studies, TV, transcription variant.

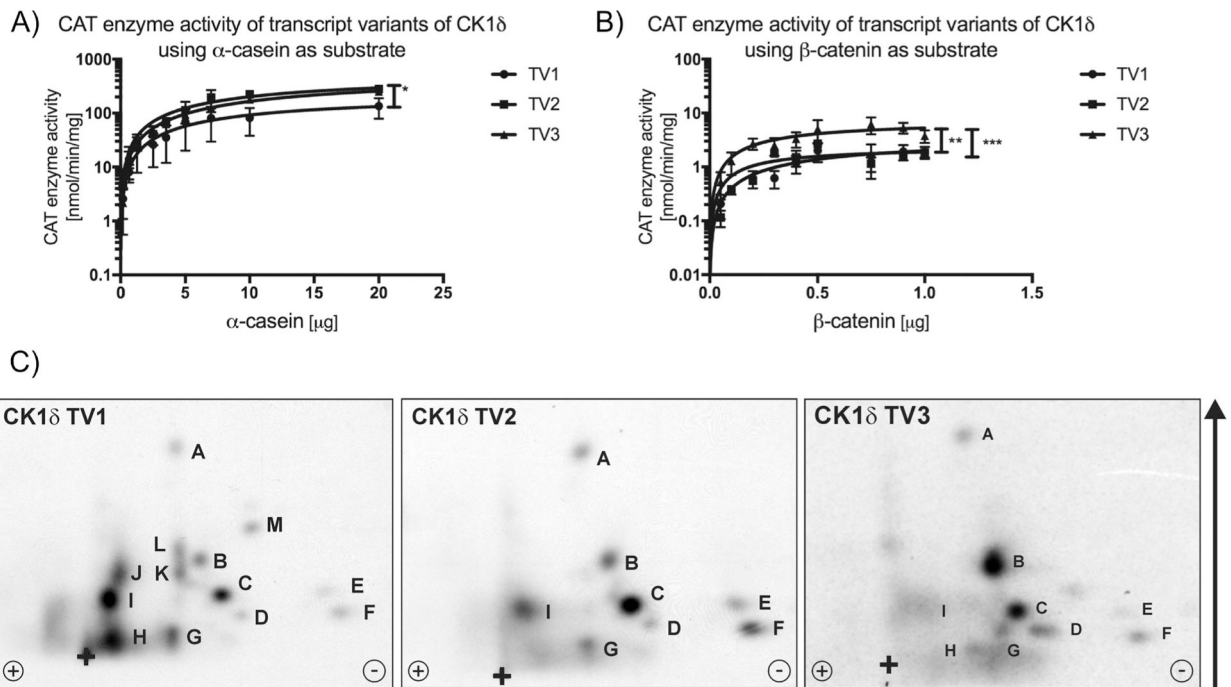


Fig. 7.

The three transcription variants of CK1δ show significant differences in their kinetic parameters and their (auto-)phosphorylation status. Catalytical (CAT) enzyme activity [nmol/min/mg] was used as readout after having performed *in vitro* kinase reactions using radioactively labeled ATP to identify the amount of phosphorylated α-casein (A) and β-catenin (GST-β-catenin¹⁻¹⁸¹) (B) of the three identified CK1δ TVs. Statistically significant differences between the whole curves of the TVs were tested by a Kruskal-Wallis test using an uncorrected Fisher's LSD test as follow-up. * indicates $p < 0.05$, ** indicates $p < 0.01$, and *** indicates $p < 0.001$. (C) Analysis of the phosphorylation status of the different CK1δ transcription variants after autophosphorylation by two dimensional phosphopeptide analysis. The phosphopeptide analysis of TV3 clearly shows differences in major and minor phosphopeptides compared to the phosphopeptide maps of TV1 and TV2. Phosphopeptides A-E are present in all three CK1δ transcription variants, whereas phosphopeptides L, K, J, and M were only observed for TV1. Phosphopeptides O and N are only present in TV3. Figure panels in (C) showing phosphopeptide maps of CK1δ TV1 and TV2 are a derivative of "Fig. 2" published in Bischof et al. (2012), used under CC BY 4.0 (<http://creativecommons.org/licenses/by/4.0/>). CAT, catalytical; TV, transcription variant.

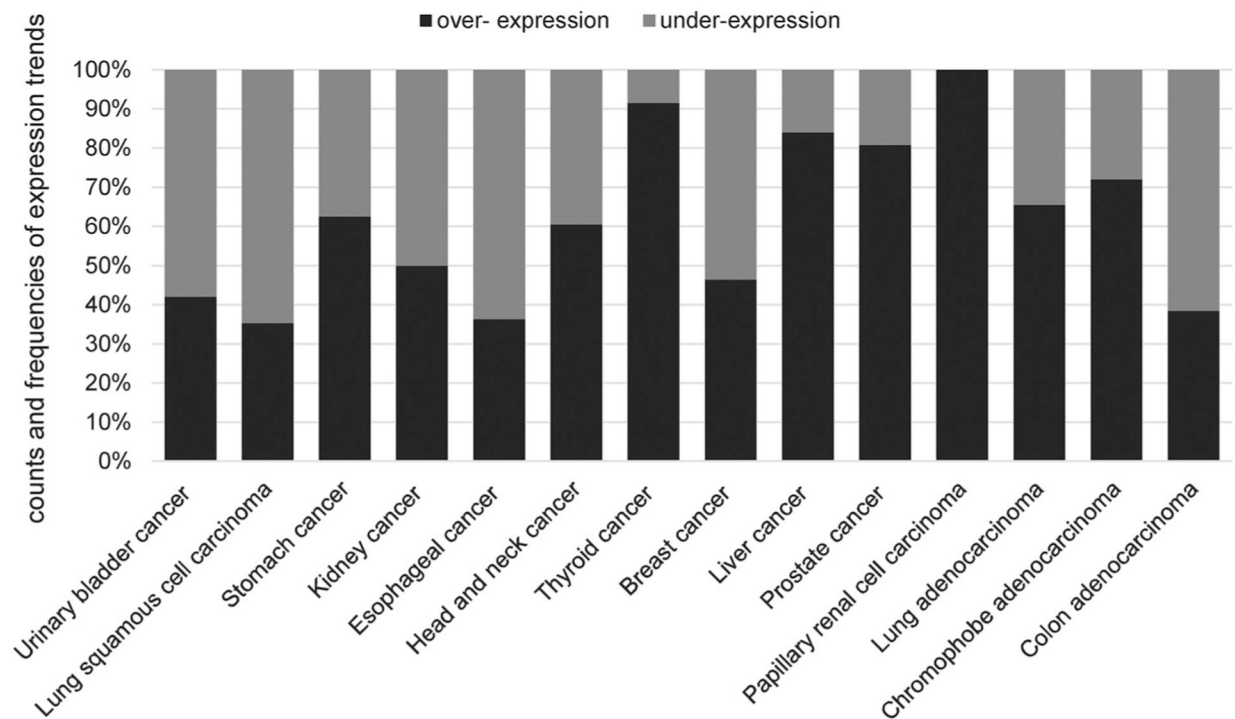


Fig. 8.

Expression trend frequency of different cancer types. Frequencies of patients following each expression trend for CK18 are presented for all relevant cancer types. For each patient, \log_2 fold-change (\log_2FC) values greater than zero were considered to follow an over-expression trend, less than zero to follow an under-expression trend. Patients with $\log_2FC = 0$ were excluded from the dataset. Note that all patients are included in this graphic, irrespective of statistical significance of the trend. Data is based on the BioXpress online tool (Wan et al., 2015; Dingerdisen et al., 2018).

Chronological overview of NCBI data bank entries of CK1δ in various organisms. The list includes the species, the name of the protein, the GI number, the amount of amino acids, and the reference, where the sequence was first published. Aa, amino acid; TV, transcription variant.

Table 1

Species	Name	GI-number	aa	Reference
<i>Saccharomyces cerevisiae JAY291</i>	HRR25	256272813	494	(DeMaggio et al., 1992)
<i>Rattus norvegicus</i>	CK1δ	294525	428	(Graves et al., 1993)
<i>Caenorhabditis elegans</i>	CK1δ	379657083	315	(Consortium, 1998)
<i>Drosophila melanogaster</i>	CK1 homolog	3335146	440	(Kloss et al., 1998)
<i>Rattus norvegicus</i>	CK1δ	14422451	415	(Takano and Nagai, 2001)
<i>Homo sapiens</i>	CK1δ TV1	13097702	415	(Strausberg et al., 2002)
<i>Homo sapiens</i>	CK1δ TV2	16041786	409	(Strausberg et al., 2002)
<i>Mus musculus</i>	CK1δ CRA a	148702868	415	(Mural et al., 2002)
<i>Mus musculus</i>	CK1δ CRA b	148702869	428	(Mural et al., 2002)
<i>Mus musculus</i>	CK1δ CRA c	148702870	409	(Mural et al., 2002)
<i>Xenopus laevis</i>	CK1δ	148229581	415	(Klein et al., 2002)
<i>Danio rerio</i>	CK1δa	157280839	403	(Albomoz et al., 2007)
<i>Danio rerio</i>	CK1δb	157280837	409	(Albomoz et al., 2007)
<i>Homo sapiens</i>	CK1δ TV3	1393428169	427	(Huang et al., 2018)

Table 2

K_m [μg] and V_{max} [nmol/min/mg] of CK1 δ TV1, TV2, and TV3 using α -casein as well as β -catenin as substrates. Values were calculated using a non-linear Michaelis-Menten fit. K_m , Michaelis constant; TV, transcription variant; V_{max} , maximum enzyme reaction velocity.

CK1 δ variant	α -Casein		β -Catenin	
	K_m [μg]	V_{max} [nmol/min/mg]	K_m [μg]	V_{max} [nmol/min/mg]
TV1	15.54	236.02	0.8121	3.63
TV2	17.21	548.88	0.2527	2.37
TV3	24.86	576.60	0.3885	7.33

Table 3

CK1δ-specific substrates. Substrates reported for CK1δ-targeted phosphorylation (*in vitro* and *in vivo*) are listed and grouped according to their associated functions. Only substrates reported for human CK1δ or appropriate orthologous proteins (*e.g.* in yeast species) are included.

Substrates	References
<i>Cancer-associated proteins:</i>	
– Adenomatous polyposis coli (APC)	(Gao et al., 2002)
– Axin	(Gao et al., 2002)
– β-Catenin	(Amit et al., 2002)
– Full-length cubitus interruptus (Ci-155)	(Price and Kalderon, 2002)
– Dishevelled (Dvl)	(Gao et al., 2002)
– Nucleoside diphosphate kinase A (nm23-H1)	(Garzia et al., 2008)
– Dapper1a (Dpr1a)	(Teran et al., 2009)
– Fat	(Sopko et al., 2009)
– Deoxycytidine kinase (dCK)	(Smal et al., 2010)
– Yes-associated protein (YAP)	(Zhao et al., 2010)
– Metastasis suppressor 1 (MTSS1)	(Zhong et al., 2013)
– Neural precursor cell expressed developmentally down-regulated protein 4 (NEDD4)	(Liu et al., 2014)
– Sprouty2 (SPRY2)	(Yim et al., 2014)
<i>Control of mitotic or meiotic processes:</i>	
– Meiotic recombination protein Rec8 (Rec8)	(Ishiguro et al., 2010)
– Endogenous meiotic inhibitor 2 (Emi2)	(Isoda et al., 2011)
– Wee1	(Penas et al., 2014)
<i>Cytoskeleton-associated and scaffolding proteins:</i>	
– Annexin II/lipocortin II	(Gao et al., 2000)
– Desmoglein 2	(Gao et al., 2000)
– Keratin 17	(Gao et al., 2000)
– Microtubule-associated protein 1A (MAP1A)	(Wolff et al., 2005)
– Microtubule-associated protein 4 (MAP4)	(Behrend et al., 2000b)
– Stathmin	(Behrend et al., 2000b)
– Tau	(Behrend et al., 2000b)
– α/β-Tubulin	(Behrend et al., 2000b)
– γ-Tubulin	(Behrend et al., 2000b)
– Connexin-43 (Cx43)	(Cooper and Lampe, 2002)
– Ras homolog family members A and B	(Kawakami et al., 2008)
– End-binding 1 (EB1)	(Zyss et al., 2011)
– Sid4	(Johnson et al., 2013)
– Ran-binding protein in the microtubule-organizing center (RanBPM)	(Wolff et al., 2015)
<i>DNA-/RNA-associated proteins:</i>	
– Chromatin-associated protein swi6 (Swi6)	(Ho et al., 1997)
– Heterogeneous nuclear ribo-nucleoprotein A1 (hnRNP A1)	(Gao et al., 2000)
– Putative RNA helicase	(Gao et al., 2000)

Substrates	References
– Nuclear factor of activated T cells 1, 2, and 4 (NFAT1, 2, 4)	(Okamura et al., 2004)
– Forkhead box G1 (FoxG1)	(Regad et al., 2007)
– Topoisomerase I α (TOP2A)	(Grozav et al., 2009)
– DNA methyltransferase 1 (Dnmt1)	(Sugiyama et al., 2010)
– Ubiquitin-like containing PHD and RING finger domains 1 protein (UHRF1)	(Chen et al., 2013)
– Yeast sterol regulatory element-binding protein homolog (Sre1N)	(Brookheart et al., 2014)
<i>Golgi- and vesicle-associated proteins:</i>	
– ADP-ribosylation factor GTPase-activating protein (ARF GAP1)	(Yu and Roth, 2002)
– Snapin	(Wolff et al., 2006)
– Protein kinase D2 (PKD2)	(von Blume et al., 2007)
– Synaptic vesicle protein 2A (SV2A)	(Zhang et al., 2015a)
<i>Mediators of cellular stress:</i>	
– Tumor protein 53 (p53)	(Knippschild et al., 1997)
– Murine double minute 2 homolog (Mdm2)	(Winter et al., 2004)
– Hypoxia-inducible factor 1 α (HIF-1 α)	(Kalousi et al., 2010)
<i>Proteins associated to neurodegenerative processes:</i>	
– Presenilin-2 (PS-2)	(Walter et al., 1998)
– Cyclin-dependent kinase 5 (CDK5)	(Sharma et al., 1999)
– α -Synuclein	(Okochi et al., 2000)
– β -Secretase (BACE1)	(Walter, Fluhner et al. 2001)
– Parkin	(Yamamoto et al., 2005)
– Cyclic AMP response element-binding protein (CREB)	(Shanware et al., 2007)
– Myelin basic protein (MBP)	(Kawakami et al., 2008)
– TAR DNA-binding protein of 43 kDa (TDP-43)	(Nonaka et al., 2016)
<i>Receptors and receptor-associated proteins:</i>	
– Transmembrane tumor necrosis factor α (mTNF α)	(Watts et al., 1999)
– Amplified in breast cancer 1 (AIB1)	(Giamas et al., 2009)
– Estrogen receptor α (Era)	(Giamas et al., 2009)
– Adiponectin	(Xu et al., 2015)
<i>Regulation of circadian rhythm:</i>	
– Period circadian protein homolog 1–2	(Camacho et al., 2001)
– Cryptochromes 1 (CRY1) and 2 (CRY2)	(Walton et al., 2009)
– Proliferator-activated receptor γ co-activator 1 α (PGC-1 α)	(Li et al., 2011b)
<i>Ribosome-related proteins:</i>	
– Nucleolar protein 56 (Nop56)	(Gao et al., 2000)
– Ribosomal proteins L4 (RPL4), L8 (RPL8), L13 (RPL13)	(Gao et al., 2000)
– Eukaryotic initiation factor 6 (eIF6)/Tif6p49	(Biswas et al., 2011)
– Essential nuclear protein 1 (ENP1)/bystin-like protein (BYSL)	(Zemp et al., 2014)
– LTV1	(Zemp et al., 2014)
<i>Viral proteins:</i>	
– Human cytomegalovirus phosphoprotein (ppUL44)	(Alvisi et al., 2011)
– Human herpes virus (HHV) E3 ubiquitin ligase (ICP0)	(Chaurushiya et al., 2012)

Substrates	References
– Simian virus 40 large T-antigen (SV40 T-Ag)	(Hirner et al., 2012)

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Table 4

Interaction partners of CK1δ. In case interaction was confirmed by co-immunoprecipitation, yeast two-hybrid screen, or similar approaches reported interaction partners for CK1δ are listed in the following table. Furthermore, information is provided if the respective protein is target for CK1δ-mediated phosphorylation (●: yes, -: no). In case the respective protein is only phosphorylated by isoforms other than CK1δ or only single family members of the indicated interaction partners are target for CK1δ-mediated phosphorylation this information is provided in parentheses.

Protein	Phosphorylation by CK1(S)	References
14-3-3 ζ	- (● CK1α)	(Dubois et al., 1997, Zemlickova et al., 2004)
AKAP450 (A-kinase anchor protein 450)	-	(Sillibourne et al., 2002)
Atoh1 (atonal bHLH transcription F factor1)	●	(Cheng et al., 2016)
Axin 1 and 2	●	(Anmit et al., 2002, Gao et al., 2002)
Chk1 (checkpoint kinase 1)	-	(Bischof et al., 2013)
CK1BP (casein kinase-1 binding protein)	●	(Yin et al., 2006)
CPL-17 (protein kinase C-potentiated myosin phosphatase inhibitor of 17 kDa)	-	(Zemlickova et al., 2004)
DDX3X (DEAD-box RNA helicase 3 X-linked)	- (● CK1ε)	(Cruciat et al., 2013, Dolde et al., 2018)
Dvl1 (dishevelled 1)	●	(Gao et al., 2002)
EB1 (microtubule plus-end-binding protein1)	●	(Zyssh et al., 2011)
FAM83A, B, E, and H	● (FAM83H)	(Kuga et al., 2016, Wang et al., 2016, Fulcher et al., 2018)
LEF-1 (lymphocyte enhancer factor-1)	●	(Hammerlein et al., 2005)
MAP1A (microtubule-associated protein 1A)	●	(Wolff et al., 2005)
NFAT1, 2, and 4 (nuclear factor of activated T cells)	● (NFAT1)	(Okamura et al., 2004)
p53 (tumor protein 53)	●	(Milne et al., 1992, Venerando et al., 2010)
PER1 and 2 (period circadian protein homolog 1 and 2)	●	(Vielhaber et al., 2000, Lee et al., 2001, Miyazaki et al., 2004, Etchegaray et al., 2009, Shanware et al., 2011)
RanBPM (Ran-binding protein in the MTOC)	●	(Wolff et al., 2015)
Snapin (SNARE-associated protein snapin)	●	(Wolff et al., 2006)
SPRY2 (sprouty2)	●	(Yin et al., 2014)
Tau (MAPT, microtubule-associated protein tau)	●	(Behrend et al., 2000b, Li et al., 2004, Kawakami et al., 2008)

Table 5

Expression levels of CK18 in different types of cancer. Differential expression tendency of CK18 is presented for different cancers. Subject ratio was calculated by comparing the number of patients significantly over- or under-expressing CK18 to the number of patients analyzed in total. For each patient, log2 fold-change (log2FC) values greater than zero were considered to follow an over-expression trend, less than zero to follow an under-expression trend. Significance was justified based on adjusted *P* value (*P* value cutoff of 0.05). Data was obtained from BioXpress online tool (Wan et al., 2015, Dingerdisen et al., 2018).

Cancer type	Subjects ratio	log2FC	P value	Adjusted P value	Significance	Expression trend
DOID:11054/urinary bladder cancer	11/19 (57.89)	-0.25	0.046	0.095	No	Down
DOID:3907/lung squamous cell carcinoma	33/51 (64.71)	-0.06	0.351	0.402	No	Down
DOID:10534/stomach cancer	12/32 (37.5)	-0.1	0.224	0.406	No	Down
DOID:263/kidney cancer	36/72 (50.0)	-0.05	0.344	0.419	No	Down
DOID:5041/esophageal cancer	7/11 (63.64)	-0.11	0.435	0.59	No	Down
DOID:11934/head and neck cancer	17/43 (39.53)	-0.01	0.919	0.941	No	Down
DOID:1781/thyroid cancer	54/59 (91.53)	0.16	0	0.002	Yes	Up
DOID:1612/breast cancer	53/114 (46.49)	0.11	0.016	0.029	Yes	Up
DOID:3571/liver cancer	42/50 (84.0)	0.21	0.008	0.049	Yes	Up
DOID:10283/prostate cancer	42/52 (80.77)	0.09	0.04	0.071	No	Up
DOID:4465/papillary renal cell carcinoma	32/32 (100.0)	0.26	0.051	0.176	No	Up
DOID:3910/lung adenocarcinoma	38/58 (65.52)	0.08	0.207	0.717	No	Up
DOID:4471/chromophobe adenocarcinoma	18/25 (72.0)	0.03	0.741	0.977	No	Up
DOID:234/colon adenocarcinoma	10/26 (38.46)	0.04	0.663	1.000	No	Up

Table 6

Biological impact of CK1δ-specific inhibitors in animal models.

Inhibitor	Effects
PF-670462	<ul style="list-style-type: none"> Results in a phase shift in circadian rhythm in rat, mouse, monkey, and zebrafish (Badura et al., 2007; Sprouse et al., 2009; Walton et al., 2009; Meng et al., 2010; Snadja Storz et al., 2013; Kennaway et al., 2015) Blocks amphetamine-induced locomotion in rats (Li et al., 2011a) Prevents relapse-like alcohol consumption in rats (Perreau-Lenz et al., 2012) Attenuates methamphetamine-induced locomotor activity (Bryant et al., 2009) Inhibits acute and chronic bleomycin-induced pulmonary fibrosis in mice (Keenan et al., 2018) Inhibits deterioration caused by ultraviolet B (UVB) eye irradiation in a mouse model of ulcerative colitis (Hiramoto et al., 2018) Slows down accumulation of leukemic cells in the peripheral blood and spleen in a mouse model for chronic lymphocytic leukemia (CLL), thereby preventing onset of anemia; consequently, treatment with PF-670462 significantly increases overall survival (Janovska et al., 2018)
Wager-6 PF-5006739	<ul style="list-style-type: none"> Attenuates opioid drug-seeking behavior in rodents (Wager et al., 2014)
SR-3029	<ul style="list-style-type: none"> Suppresses TPA-induced skin tumor formation in a mouse model, probably through blocking Wnt/β-catenin signaling (Su et al., 2018) Results in tumor regression in orthotopic xenotransplantation models of triple-negative breast cancer (Rosenberg et al., 2015)
Salado-20, 24, 35	<ul style="list-style-type: none"> Exhibit a protective effect on <i>in vivo</i> neurotoxicity of human TDP-43 in <i>Drosophila</i> (Salado et al., 2014)